CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761180Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	December 9, 2021
Reviewer:	Catherine Lerro, PhD, MPH Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Tralokinumab (ADBRY)
Application Type/Number:	BLA 761180 / IND 123797
Sponsor:	LEO Pharma A/S
OSE RCM #:	2021-198

1. BACKGROUND INFORMATION

1.1. Medical Product

Tralokinumab (ADBRY, LEO Pharma A/S) is a new molecular entity, fully human IgG4 monoclonal antibody that neutralizes IL-13 cytokine by inhibiting interactions with IL-13 receptors α1 and α2 (LEO 2020b). It is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Tralokinumab is administered by subcutaneous injections, with or without topical corticosteroids, at the recommended initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) every other week (or every 4 weeks (b) (4) (b) (4)) (Draft Label 2021). The time to maximum concentration in serum (t_{max}) is 5 to 8 days, and the half-life is 22 days in adults (LEO 2020b). It is available in a 150 mg/mL single-dose prefilled syringe with needle guard and stored refrigerated at 2°C to 8°C in the original carton to protect from light (Draft Label 2021).

The most commonly reported treatment-related adverse events reported in clinical trials (at least one percent of tralokinumab-exposed patients) were upper respiratory infection, conjunctivitis, injection site reaction, and eosinophilia (Draft Label 2021).

As with all therapeutic proteins, there is a potential for immunogenicity with tralokinumab. Among patients in the clinical trials who received tralokinumab, incidence of antidrug antibodies, persistent antidrug antibodies, and neutralizing antibodies were 4.6%, 0.9%, and 1.0%, respectively. No clinically meaningful differences in the pharmacokinetics, safety, or efficacy of tralokinumab were observed in patients who tested positive for anti-tralokinumab antibody (Draft Label 2021).

1.2. Describe the Safety Concern

The Division of Dermatology and Dentistry (DDD) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of tralokinumab during pregnancy. Atopic dermatitis is common among women of childbearing age (Silverberg and Hanifin 2013), and exposure to tralokinumab during pregnancy may occur.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively (Dinatale 2016). The background risk of major birth defects and miscarriage for the indicated population is unknown. Observational studies have generally observed null or inverse associations between atopic dermatitis diagnosis and various pregnancy outcomes including miscarriage, pre-eclampsia, small for gestational age, and stillbirth (Seeger, Lanza et al. 2007, Trønnes, Wilcox et al. 2014). Secondary skin infection causing eczema herpeticum may, however, be associated with preterm delivery, intrauterine growth restriction, and miscarriage (Weatherhead, Robson et al. 2007).

In clinical trials for tralokinumab in atopic dermatitis (data cut-off March 31, 2020), the Sponsor identified 30 maternal pregnancy cases in the safety database. In all pregnancy cases where the woman decided to continue the pregnancy, tralokinumab treatment was discontinued (LEO 2021).

For the reported pregnancies, 13 resulted in live births (no adverse infant outcomes), 11 in elective abortion (no fetal abnormalities specified), 2 in spontaneous abortion (no fetal abnormalities specified), and 2 were ongoing as of the cut-off date. No stillbirths were reported (Limpert, Dinatale et al. 2020, LEO 2021). As of March 31, 2021, there were four new pregnancies which included one ongoing pregnancy, two elective abortions, and one spontaneous abortion. Two serious adverse events were reported in a healthy baby (jaundice and C-reactive protein increase) born at gestational week 38 via vaginal delivery without any complications and without congenital abnormalities. Both SAEs resolved within three days. The Sponsor concluded that the current data are not considered sufficient to inform about the pregnancy risks associated with tralokinumab exposure due to the limited number of pregnancies in exposed clinical trial subjects (LEO 2021).

Tralokinumab is a fully human IgG4 monoclonal antibody that specifically neutralizes the IL-13 cytokine via inhibition of the interaction with IL-13 receptors (Blanchard, Mishra et al. 2005, May, Monk et al. 2012, Thom and Minter 2012, Popovic, Breed et al. 2017). IL-13 is thought to play a role in blastocyst implantation and is found in the placenta (Chegini, Ma et al. 2002); thus theoretically tralokinumab could interfere with reproductive function.

Animal studies generally did not find evidence for reproductive or developmental toxicity (LEO 2020a). In sexually mature male and female cynomolgus monkeys, no effects were observed on fertility endpoints. A pilot study of pregnant cynomolgus monkeys found no effect of tralokinumab on embryofetal development; however substantial placental transfer of tralokinumab was evident with fetal serum concentrations ranging from 53% to 636% of the maternal serum concentrations. Two studies evaluating the effect of tralokinumab on pre-and postnatal development and maternal function in cynomolgus monkeys generally observed no adverse effects on either maternal or infant assessments. Potential tralokinumab-associated histiocytic infiltration of the spleen was observed in infants in one study; however, due to the nature of the change, incidence observed in control and treated animals, and low overall incidence and severity, the Sponsor concluded that this finding was likely non-adverse.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete General ARIA Sufficiency Template.*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☒ Electronic database study without chart review
☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case-control study.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to medical records. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations.

Covariates: ARIA does not have detailed information on potential confounders. The pregnancy registry being considered would collect detailed narratives with information on potential covariates such as severity of atopic dermatitis or family history of the disease or outcomes, and lifestyle factors such as prenatal supplements.

Analytical Tools: ARIA data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal and fetal outcomes.

2.5. Please include the proposed PMR language in the approval letter.

DDD requests two observational PMRs related to pregnancy outcomes; the proposed language (still in draft form) is as follows:

PMR ####-5:

A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tralokinumab during pregnancy to an unexposed control population. (b) (4)

(b) (4)

PMR ####-6:

An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to tralokinumab during pregnancy compared to an unexposed control population.

The finalized PMR language will be issued upon approval.

3. References

Tralokinumab (ADBRY) Draft Label, LEO Pharma, Last updated on October 25, 2021, accessed November 16, 2021.

Blanchard, C, A Mishra, H Saito-Akei, P Monk, I Anderson and ME Rothenberg, 2005, Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human-interleukin-13 antibody (CAT-354), Clin Exp Allergy, 35(8): 1096-1103.

Chegini, N, C Ma, M Roberts, RS Williams and BA Ripps, 2002, Differential expression of interleukins (IL) IL-13 and IL-15 throughout the menstrual cycle in endometrium of normal fertile women and women with recurrent spontaneous abortion, J Reprod Immunol, 56(1-2): 93-110.

Dinatale, M, Division of Pediatric and Maternal Health, FDA, The pregnancy and lactation labeling rule (PLLR), accessed May 19, 2020, from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf.

LEO, 2020a, 2.4 Nonclinical Overview, Tralokinumab in modeate-to-severe atopic dermatitis, filed under BLA 761180 on April 27, 2020.

LEO, 2020b, 2.5 Clinical Overview, Tralokinumab in moderate-to-severe atopic dermatitis, filed under BLA 761180 on April 27, 2020.

LEO, 2021, Safety Update, Tralokinumab in modeate-to-severe atopic dermatitis, filed under BLA 761180 on July 2, 2021.

Limpert, J, M Dinatale and LP Yao, 2020, Division of Pediatric and Maternal Health Review: Adtralza (tralokinumab) injection for subcutaneous use, Evaluation of post-marketing requirements (PMRs), filed under BLA 761180 on December 16, 2020 (DARRTS Reference ID: 4715000).

May, RD, PD Monk, ES Cohen, D Manuel, F Dempsey, NH Davis, AJ Dodd, DJ Corkill, J Woods, C Joberty-Candotti, LA Conroy, F Koentgen, EC Martin, R Wilson, N Brennan, J Powell and IK Anderson, 2012, Preclinical development of CAT-354, an IL-13 neutralizing antibody, for the treatment of severe uncontrolled asthma, Br J Pharmacol, 166(1): 177-193.

Popovic, B, J Breed, DG Rees, MJ Gardener, LM Vinall, B Kemp, J Spooner, J Keen, R Minter, F Uddin, G Colice, T Wilkinson, T Vaughan and RD May, 2017, Structural Characterisation Reveals Mechanism of IL-13-Neutralising Monoclonal Antibody Tralokinumab as Inhibition of Binding to IL-13Rα1 and IL-13Rα2, J Mol Biol, 429(2): 208-219.

Seeger, JD, LL Lanza, WA West, C Fernandez and E Rivero, 2007, Pregnancy and pregnancy outcome among women with inflammatory skin diseases, Dermatology, 214(1): 32-39.

Silverberg, JI and JM Hanifin, 2013, Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study, J Allergy Clin Immunol, 132(5): 1132-1138.

Thom, G and R Minter, 2012, Optimization of CAT-354, a therapeutic antibody directed against interleukin-13, using ribosome display, Methods Mol Biol, 805: 393-401.

Trønnes, H, AJ Wilcox, T Markestad, MC Tollånes, RT Lie and D Moster, 2014, Associations of maternal atopic diseases with adverse pregnancy outcomes: a national cohort study, Paediatric and perinatal epidemiology, 28(6): 489-497.

Weatherhead, S, SC Robson and NJ Reynolds, 2007, Eczema in pregnancy, Bmj, 335(7611): 152-154.

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/s/

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SARAH K DUTCHER
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ROBERT BALL
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 30, 2021

To: Hamid Tabatabai, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
David Kettl, Clinical Team Leader, DDD
Strother Dixon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for ADBRY™ (tralokinumab-ldrm) injection, for subcutaneous use

BLA: 761180

In response to DDD's consult request dated July 2, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and instructions for use (IFU) for the resubmission of the original BLA submission for ADBRY™ (tralokinumab-ldrm) injection, for subcutaneous use (Adbry).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI in Sharepoint on November 30, 2021 and are provided below.

PPI and IFU: OPDP's comments on the proposed labeling are based on the draft PPI and IFU in Sharepoint on November 30, 2021 and we have no additional comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

15 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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LAURIE J BUONACCORSI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	November 30, 2021
To:	Strother Dixon Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ADBRY (tralokinumab-ldrm)
Dosage Form and Route:	Injection, for subcutaneous use
Application Type/Number:	BLA 761180
Applicant:	Leo Pharmaceuticals Inc.

1 INTRODUCTION

On July 2, 2021, Leo Pharmaceuticals Inc., re-submitted for the Agency's review a Biologics License Application (BLA-761180) for ADBRY (tralokinumab-ldrm) Injection, for subcutaneous use, for the proposed indication of use for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. On July 12, 2021, the Division of Dermatology and Dentistry (DDD) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ADBRY (tralokinumab-ldrm) Injection, for subcutaneous use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPI and IFU for ADBRY (tralokinumab-ldrm) Injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft ADBRY (tralokinumab-ldrm) PPI-IFU received on July 2, 2021 and received by DMPP on October 25, 2021.
- Draft ADBRY (tralokinumab-ldrm) Prescribing Information (PI) received on July 2, 2021 and received by DMPP on October 25, 2021.
- ADBRY (tralokinumab-ldrm) PPI-IFU review dated December 15, 2020.

3 CONCLUSIONS

We find the Applicant's proposed PPI-IFU are acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI-IFU.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	10/13/2021		
To:	Strother Dixon		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	Other
From	Stephen M. Retta OPEQ/OHT3/DHT3C		
Through (Team)	Suzanne Hudak, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C GHDB		
Subject	BLA 761180, (b) (4) (Tralokinumab) ICC2100604 CR response from 4/23/2021, ICC2000441		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 2/4/2021 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761180
Sponsor	Leo Pharma Inc.
Drug/Biologic	(b) (4) (Tralokinumab)
Indications for Use	is proposed for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately contolled with topical prescription therapies or when those therapies are not advisable.
Device Constituent	Pre-Filled Syringe
Related Files	BLA 761180

Important Dates	
Filing	June 11, 2020
74-Day Letter	June 22, 2020
Midcycle Meeting/IRs due	September 25, 2020
Final Lead Device Review Memo Due	November 2, 2021
PDUFA Date	December 30, 2021

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

3. PURPOSE/BACKGROUND

3.1. Scope

Leo Pharma Inc. is requesting approval of a prefilled syringe (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The device constituent of the combination product is a Pre-Filled Syringe.

Choose an item. has requested the following consult for review of the device constituent of the combination product:

Please review the device component of this original BLA submission.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- ☒ Device performance
- ☒ Biocompatibility of the patient contacting components
- ☐ Sterility
- ☒ Stability – device performance on stability
- ☒ Essential Performance Requirements (EPR) Control strategy
- ☐ Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

CR Letter 4/23/2021 under ICC2000441:
CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:
Major Deficiencies:

1. You provided a response to an information request dated, December 14, 2020, which provided documentation of (b) (4) (b) (4) associated 510(k) references to address our request for data verifying the needle safety performance of your combination product at an appropriate reliability limit (95% confidence /99% reliability) and pre-conditioning (aging, drop testing and shipping). While the testing provided evidence for performance of the 510(k) cleared needle safety device component, the testing did not include testing of your final finished combination product or testing after the requested representative preconditioning (aging of the device, dropping of the device, and simulated shipping). You also provided additional information in your Late-Cycle background package dated January 22, 2021, where you asserted that The (b) (4) is a 510(k) FDA cleared medical device that is manufactured by (b) (4)
   - This device has been cleared by the FDA to provide protection from accidental needle stick injury.
   - It has been commercially marketed worldwide since 2001 with numerous products.
   - A study evaluating the (b) (4) device is summarized in the attached document from (b) (4) demonstrating 512 successful device safety feature activation with 0 failures.

Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, design differences between your final finished combination product and currently marketed products, combination product manufacturing and preconditioning would impact the performance and reliability. Failure of the needle safety device to perform adequately may result in serious risks (accidental contaminated needle sticks). Provide testing demonstrating that your final finished combination product needle safety performance (needle safety activation and lockout) can meet a confidence and reliability of 95%/99% after aging of the device to the proposed shelf-life, drop testing and simulated shipping per ASTM 4169-16 *Standard Practice for Performance Testing of Shipping Containers and Systems* sequentially.

The recommended confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download.

A review of the CR deficiencies begins on page 23 of the review memo.

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
(b) (4) (Tralokinumab)	The APFS is intended to deliver a 1 mL injection of tralokinumab via subcutaneous delivery to patients with moderate to severe atopic dermatitis (AD).
Pre-Filled Syringe	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	3.2.R
0001	3.2.P
0022	3.2.R.3.4.7
0033	3.2.R.3.4.8
0041	3.2.R

4. DEVICE DESCRIPTION

4.1. Device Description

From 3.2.R.3 reg-info-device-discription. The combination product consists of an **accessorized prefilled syringe** (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab.

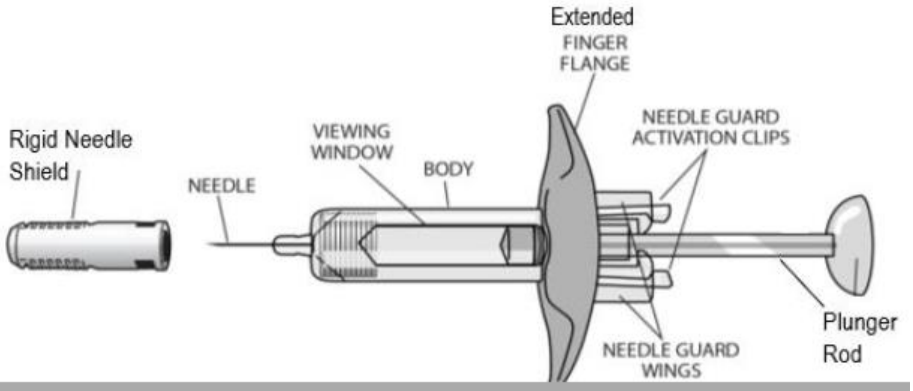
One intended user population includes HCPs administering tralokinumab to patients in a clinical use environment.
A second intended user population includes patients performing self-administration and caregivers performing third party administration to patients. It is intended that patients and caregivers will use th APFS in a non-clinical environment, most commonly at home.

The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function. It is designed to administer a 1 mL fixed dose of 150 mg/mL tralokinumab, 2 × 1 mL APFS provides one full 300 mg dose. The APFS is supplied pre-assembled and ready for use.

The APFS consists of a prefilled syringe sub-assembly (PFS-SA) consisting of a 1 mL long syringe barrel with a ½ inch **27 gauge** (b) (4) **needle**, rigid needle shield(RNS) and plunger stopper. The accessorized part consists of a needle safety guard, plunger rod and extended finger flange. The needle safety guard is composed of a needle guard body with activation clips and wings.

The prefilled syringe is (b) (4) in needle.

Figure 1 **Schematic drawing of the APFS**



(b) (4)

The intended route of administration is by subcutaneous injection. Injection sites for HCP or caregiver are abdomen, thigh or upper arm. Injection sites for self-administration are abdomen or thigh.

The APFS conditions of use are described in Table 1.

Table 1 APFS Conditions of Use

Biologic product for injection	Tralokinumab, for subcutaneous injection
Dosage capability	APFS dose: 1 mL (150 mg/mL). Total dose per treatment: 2 mL (2 × 150mg/mL → 300 mg in total)
Method of injection	Manual delivery
Packaging configuration	Paperboard box
Environment of use conditions	Non-clinical or clinical environments
Recommended Storage	Store refrigerated at 36°F to 46°F (2-8°C) in the original carton. Do not freeze.
Handling	Acclimate to room temperature 68°F to 77°F ((b) (4) 25°C) for at least 30 minutes before use. Protect from direct sunlight.

Table 2 APFS Description of Components and Materials of Construction

Component	Function	Material	Supplier
PFS-SA			
Syringe barrel	Primary container for drug product	(b) (4) Type I glass	(b) (4)
Needle		(b) (4)	
Plunger stopper			
Rigid Needle shield (b) (4)			
Rigid needle shield (b) (4)			
Accessories			
Extended finger flange			
Guard			
Spring			
Body			
Plunger rod			

4.2. Design Requirements

Basic Syringe Description/Requirements

Requirement	Reviewer Comment
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Health Care Proferssionals administering tralokinumab to patients in a clinical use environment. Patients performing self-administration and caregivers performing third party administration to patients. It is intended that patients and caregivers will use th APFS in a non-clinical environment, most commonly at home.
Injection Site	The intended route of administration is by subcutaneous injection. Injection sites for HCP or caregiver are abdomen, thigh

	or upper arm. Injection sites for self-administration are abdomen or thigh.
Injection tissue and depth of injection	Subcutaneous injection
Type of Use (e.g. single use, disposable, reusable, other)	The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function.
Environments of use (e.g. home, clinic)	Clinical Use environment or home use.
Storage conditions and expiry	Store refrigerated at 36°F to 46°F (2-8°C) in the original carton. Do not freeze.
Needle connection (e.g. luer, slip tip, staked)	(b) (4)
Syringe Volume	1 ml
Device materials including lubricant	Syringe Barrel is (b) (4) Type I glass, (b) (4) needle, Plunger stopper (b) (4) needle shield (b) (4) Rigid needle shield (b) (4) (b) (4) See table 2 above and 3.2.P drug-product p. 36/41

Additional Syringe Description/Requirements

Requirement	Reviewer Comment
Hypodermic Needle: length, gauge, and configuration of the tip.	1 mL long glass barrel with a ½ inch 27G STW needle with RNS
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility criteria (for insulin syringes). Insulin Syringes: The scale on the barrel should be in units of insulin.	The APFS does not contain graduation markings as it is intended to deliver the full labeled volume i.e., the APFS is single use for a fixed dose.
Reuse Durability (for reusable piston syringes): number of times the device can be sterilized and still meet specifications (using sterilization method indicated in the labeling).	N/A
Safety Features (e.g. Needle safety component/device)	The PFS-SA is assembled with a needle safety guard to protect the user from unintended needle stick injuries. The needle safety guard design provides (b) (4) of the safety mechanism to cover the needle following injection.
Automated Functions	N/A
Sterilization method	N/A

*See Design Verification Section for verification of design requirements

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor provided an adequate device deciption for the Pre-Filled Syringe prefilled (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☑

5.1. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☐ Yes ☐ No ☑ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection Needed ☐ N/A
CDRH completed a review of the Quality Systems	☐ Yes ☐ No ☐ N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in Appendix B

5.2. Filing Recommendation

FILING REVIEW CONCLUSION
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☑ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☑ N/A **Site(s) needing inspection:**
Reviewer Comments
Refuse to File Deficiencies: ☐ Yes ☐ No ☑ N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No ☑ N/A

☐ **No Additional Information Requests to add**

6. DEVICE PERFORMANCE REVIEW

6.1. Design Verification/Validation

6.1.1. Device Specification Standards and Guidance Documents

Syringe		**Data Adequate**		
		Yes	**No**	**N/A**
Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☑	☐	☐
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☐	☐	☑
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☑
Needle/Sharps		**Data Adequate**		
		Yes	**No**	**N/A**
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☐	☐	☑
Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☐	☐	☑
Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	☐	☐	☑
Luer Lock		**Data Adequate**		
		Yes	**No**	**N/A**
Connection	ISO 80369-7, Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications **(replaces ISO 594-1 and 594-2 as of 2020) ISO 594-1, Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 1: General requirements ISO 594-2, Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 2: Lock fittings	☐	☐	☑
Other		**Data Adequate**		
		Yes	**No**	**N/A**
[Other]	[Other]	☐	☐	☐

6.1.2. Device Performance Evaluation

3.2.R Device Design Verification

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy/ Delivered Volume	The combination product shall deliver a dose volume (b) (4) mL	Y. Accept of 95%C/97.5%Rtolerance interval, V (b) (4) mL Results: n = 60 min = (b) (4) max = mean StDev	Y. Data provided to support dose volume (b) (4) mL in 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/97.5%Rtolerance interval, V (b) (4) n = 60 min = (b) (4) max = mean StDev
Break loose Force	Maximum break loose force (b) (4)	Y. A constant injection rate/ compression speed (b) (4) mm/min) is applied to each syringe tested. Accept on 95%C/90%R tolerance interval, Requiring a sample size of 60, F (b) (4) Results:n = 60 min = 5N max = 8N mean = 7N StDev = 1N	Y. Data provided to support Maximum break loose force (b) (4) in 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/90%R tolerance interval, F (b) (4) n = 29 min = 6N max = 9N mean = 7N StDev = 1N
Glide Force	Maximum glide force (b) (4)	Y. A constant injection rate/ compression speed (b) (4) mm/min) is applied to each syringe tested. Accept on 95%C/90%R tolerance interval, Requiring a sample size of 60, F (b) (4) Results: n = 60 min = 6N	Y. Data provided to support Maximum glide force (b) (4) n 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/90%R tolerance interval, F (b) (4) n = 29 min = 6N max = 8N mean = 7N

		max = 9N mean = 8N StDev = 1N			StDev = 0N
Cap Removal Force	Not applicable	N/A		n/a	n/a
Rigid needle shield pull-off force	The combination product shall have a rigid needle shield pull-off force that is (b) (4)	Y. 95%C/90%R tolerance interval, (b) (4) Results: n = 46 min = 18N max = 24N mean = 21N StDev = 1N	Y. Data provided to support rigid needle shield pull-off force that is (b) (4) in 3 lots	N/A	Y. Accept on 95%C/90%R tolerance interval, (b) (4) n = 46 min = 18N max = 23N mean = 21N StDev = 1N
Needle safety feature activation	(b) (4)	Accept on 0 failures. Reject on 1 or more failures	Y, n = 300 pass = 300 fail = 0	Y, Accept on 0 failures. Reject on 1 or more failures n = 300 pass = 300 fail = 0	Y, Accept on 0 failures. Reject on 1 or more failures n = 300 pass = 300 fail = 0
Needle access after injection		(b) (4) Accept on 0 failures. Reject on 1 or more failures	n = 29 pass = 29 fail = 0	N/A	n = 300 pass = 300 fail = 0
Needle safety feature override force after injection		Accept on 95%C/90%R tolerance interval, F (b) (4)	Y, n = 30 min = 118N max = 125N mean = 130N StDev = 3N	n = 30 min = 118N max = 125N mean = 130N StDev = 3N	n = 30 min = 118N max = 125N mean = 130N StDev = 3N

Device Free Fall	(b) (4)	No breakage to PFS-SA Accept on 0 failures. Reject on 1 or more failures Deliverable volume V (b) (4) mL Accept on 95%C/97.5%R tolerance interval, V (b) (4) mL (b) (4) Accept on 0 failures. Reject on 1 or more failures	n = 40 pass = 40 fail = 0 min = 1.0mL max = 1.1mL mean = 1.1mL StDev = 0.0mL n = 40 pass = 40 fail = 0	N/A	N/A

Reviewer Comment

The device design verification testing is acceptable. Results include dose accuracy/Delivered volume, Break Loose Force, Glide Force, and Rigid needle shield pull-off force.

3.2.P.2.4.2.4 Performance

"The essential performance requirements of the combination product was evaluated via functionality (break loose and glide force) and deliverable volume tests that were performed as part of specified Drug Product stability studies (M3.2.P.8.1). A summary of the initial (time zero) results are shown in Table 9. The results show that the maximum break loose force, maximum glide force, and deliverable volume were reproducible and consistent between Drug Product lots. The performance of the container closure system was demonstrated to be suitable for injection." P. 16, 3.2.P.2.4 Container Closure System

Table 9 Summary of Container Closure Performance

Stability Lot Number (Stability Protocol Number)	Maximum Break Loose Force (N)	Maximum Glide Force (N)	Deliverable Volume (mL)
83205.145 (DSP-35436)			
002G13 (DSP-35437)			
ML00029-35 (DSP-354309)			

(b) (4)

Analytical procedures for Break Loose Force and Glide Foce is summarized in 3.2.P.5.2 Analytical Procedures

6.1.3. Stability Review Summary

Shelf-life:	shelf life of 36 months for drug product
Storage **conditions**:	storage condition of 5°C
Time period and storage conditions provided for accelerated aging:	25°C ± 2°C/60% ± 5% RH is an accelerated condition
Time period and storage conditions provided for real-time aging:	Storage condition of 5°C with testing scheduled at 0, 3, 6, 9, 12, 18, 24, 36 months and with additional 48 and 60 months for some primary lots. (3.2.P stability summary)

*Endpoint evaluation is provided in section 6.1.2.

Stability studies are monitored at four conditions:

- (b) (4)°C condition evaluates stability at the temperature at which the Drug Substance (long-term storage condition)
- (b) (4)°C condition evaluates stability at a short term recommended storage condition
- (b) (4)% RH is an accelerated condition
- % RH is a stressed condition

3.2.S.7.1 Stability Summary and Conclusions

The proposed Drug Substance shelf life is (b) (4) months at the long-term storage condition of (b) (4)°C in (b) (4) based on the following:

- (b) (4) months of existing real time data on commitment lots.
- months of real-time data from 2 primary lots (BL2136, 72635-106), (b) (4) months of realtime ta from 3 more primary lots (HL2758, HL2777, HN2204), and (b) (4) months of realtime

data from 1 more primary lot (KJ0190).

The proposed Drug Substance shelf life is [redacted] months at the short term storage condition of [redacted] °C in [redacted] based on the following:

- [redacted] months of real time data on commitment lots.
- [redacted] months of real-time data from primary lots (BL2136, 72635-106, HL2758, HL2777, HN2204, and KJ0190).

The proposed Drug Substance shelf life is [redacted] months in total in [redacted] This [redacted] months may be apportioned under a combination of two storage conditions as follows:

- [redacted] months at the long-term storage condition of [redacted] °C.
- [redacted] months at the short-term storage condition of [redacted] °C, noting Drug Substance may [redacted]

Statistial justification of a sample size of N=60 is provided in 3.2.R.3.4 Design Verification Overview

3.2.P.8.3 Stability Data

From three separate lots:
Real time aging under recommended storage conditions of 5°C is provided for 60 months. This is enough to support the 36 month shelf life. BLF abd GF samples below. Dlivered Volume was also supported up to 60 months with dose volume [redacted] mL

Table 3 Stability Results for Primary Lot 011G13A (150 mg/mL): Device Functionality Testing

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
Acceptance criteria	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)
5°C ± 3°C							
0	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]
3	[redacted]						
6							
12							
18							
24							
36							
48							
60							
25°C ± 2°C / 60% ± 5% RH							
0							
1							
3							
6							

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
40°C ± 2°C / 75% ± 5% RH							
0	(b) (4)						
1							
3							

RH = relative humidity;

NP = not performed per the stability protocol

[a] Initial timepoint testing for rigid needle shield removal force and break loose glide force assays were inadvertently not performed. Investigation was conducted and the root cause was inadequate documentation upon shipment of samples for testing.

Table 3 Stability Results for Primary Lot 83205.145: Device Functionality Testing

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
Acceptance criteria	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)
5°C ± 3°C							
0	(b) (4)						
3							
6							
12							
18							
24							
30							
36							
42							
48							
60							
25°C ±2°C / 60% ± 5% RH							
0							
1							
3							
6							

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
40°C ± 2°C / 75% ± 5% RH							
0	(b) (4)						
1							
3							

RH = relative humidity

Reviewer Comments

The sponsor provides stability data for the device with evaluation of shield removal force, Break loose force, and Glide force. The results are acceptable.

The device has (b) (4) needle safety device. The sponsor appears to have evaluated this function per the ISO 23908 standard. Some functions include; Needle safety activation, Needle safety lockout. Both need to be verified after shelf-life, shipping and drop testing. Reliability should be 99%, not 90% per FDA guidance (https://www.fda.gov/media/71142/download)

Needle safety may have been covered through glide force but the reliability should be 99%, not 90% per FDA guidance (https://www.fda.gov/media/71142/download)

An IR was recommended:

1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons:

   The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required.

   Furthermore, the testing should also be performed afrer aging of the device, dropping of the device, and simulated shipping.

   This confidence and reliability information for sharps injury prevention devices can be found in *FDA Guidance: Medical Devices with Sharps Injury Prevention Features* https://www.fda.gov/media/71142/download

An IR was issued December 14, 2020 in CR#3. The response was not adequate. The sponsor provided documentation of the testing of the (b) (4) which was approved through 510(K). This teting is provided, however, the testing does not appear to include any testing with aging of the device (Shelf-Life), dropping of the device, and simulated shipping. It is not clear if the testing is the final manufactured design of the proposed device. Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, combination product manufacturing and preconditioning may impact the performance.

6.1.4. Biocompatibility Evaluation

☑ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]

☐ Biocompatibility was not evaluated **because**: Click or tap here to enter text.

Contact Type and Duration:	Surface-contacting, skin – limited exposure up to 24 h.
Test article:	Syringe Barrel, Needle, Needle adhesive, Plunger stopper, Rigid Needle Shield, (b) (4)
Endpoints Evaluated:	Cytotoxicity, Skin sensitization, Systemic Toxicity (Pyrogenicity), Selection of tests for interactions with blood (not specified)

Extraction Method and Test Methods Acceptability:	Report not provided.

Reviewer Comment

The sponsor claims conformance to Biocompatibility testing (ISO 10993), however, the reports of the testing are not provided. The syringe barrel, , Needle, Needle adhesive, Plunger stopper, are within the fluid patch of the drug and an evaluation of these components is deferred to CDER. However, the Extended finger flange, Needle safety guard, and Plunger rod are not in direct contact with the drug substance and will be evaluated as part of this memo. The sponsor notes Cytotoxicity and Skin sensitization testing, that the testing conforms to the criterion of ISO 10993, however reports are not provided. Classification for the device as a surface device contacting intact skin (Per the 2016 FDA guidance Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" and ISO 10993-1, the Sponsor should evaluate the following endpoints for the plunger: Cytotoxicity, Sensitization, and Irritation. Since the Sponsor has not submitted any report all reports should be submitted. Furthermore,the sponsor does not indicate that skin irritation testing has been performed on the skin contacting components. An information request will be issued to the Sponsor.

Table 16 Primary packaging component materials

Component	Description	Material of Construction	Compliance
Syringe barrel		Type I (b) (4) glass	USP <660>, Ph. Eur 3.2.1, and JP 7.01
Needle	(b) (4)		ISO 9626
Rigid needle shield (b) (4)			
Rigid needle shield (b) (4)			USP <381> and Ph. Eur. 3.2.9
Adhesive			USP <88>
(b) (4)			(b) (4) Ph. Eur. 3.1.8
Plunger stopper			USP <381>, USP <87>, USP <88> and Ph.Eur 3.2.9.
(b) (4)			(b) (4) Ph. Eur. 3.1.8

Table 17 Device components

Accessory component	Material of Construction	Compliance
Needle safety guard	(b) (4)	ISO 10993 materials for surface contact <24 hours
Extended finger flange		ISO 10993 materials for surface contact <24 hours
Plunger rod		ISO 10993 materials for surface contact <24 hours

	Date Sent: 10/2/2020	Date/Sequence Received: 10/30/2020
Information Request #1	1. For the extended finger flange, needle safety guard, and plunger rod, which are intact skin contacting, you provide Cytotoxicity and Skin sensitization testing, that you indicate conforms to the criterion of ISO 10993, however you do not provide	

<table>
<tr><td></td><td>reports to verify that conformance. Furthermore, per FDA guidance Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process” the appropriate endpoints based on your contact classification are: Cytotoxicity, Sensitization, and Irritation. Therefore, please provide testing reports for cytotoxicity, sensitization, and irritation for the extended finger flange, needle safety guard and plunger rod.</td></tr>
<tr><td>Sponsor Response</td><td>The device components extended finger flange, needle safety guard and plunger rod have been tested for cytotoxicity, sensitization and irritation according to ISO 10993-5 “Biological Evaluation of Medical Devices Part 5: Tests of In Vitro Cytotoxicity” and ISO 10993-10 “Biological Evaluation of Medical Devices Part 10: Tests for Irritation and Skin Sensitization” Reports containing the results of biocompatibility testing to verify conformance with ISO 10993 are included in module 3.2.R.3.5.3.</td></tr>
<tr><td>Reviewer Comments</td><td>The sponsor provided summary test reports in the response Module 3.2.R.3.5.3 Device Biological Evaluation, Reg-info-dbe and files with Nov. 1, 2020 response. The sponsor tested the finger flange, needle safety guard, and plunger rod for biocompatibility with in vitro Cytotoxity, Skin Irritation, and Skin sensitization according to ISO 10993, part 5 and part 10 as appropriate.

The plunger rod reported in reg-info-cs-01
Studies results summary for TA_12T_50471 [redacted](b) (4) Plunger Rod): qualification of the [redacted](b) (4) plunger rod.

IN VITRO STUDIES, Test Article 12T_50471
<table><tr><th>Test</th><th>Results</th></tr><tr><td>ISO 10993-5
Cell Cytotoxicity Elution Test</td><td>Cytotoxicity: none
Score = 0</td></tr></table>
IN VIVO STUDIES, Test Article 12T_50471
<table><tr><th>Test</th><th>Results</th></tr><tr><td>ISO 10993-10
Intracutaneous Reactivity</td><td>Negligible Irritant
Score = 0.0 (SAL) / Score = 0.1 (SO)</td></tr><tr><td>ISO 10993-10
Guinea Pig Maximization Test</td><td>Nonsensitizer
Score = 0 (SAL, SO)</td></tr></table>
The needle safety guard reported in reg-info-cs-02</td></tr>
</table>

***IN VITRO* STUDIES, Test Article 17-6200-016**

Test	Results
ISO 10993-5 Cell Cytotoxicity Elution Test	Cytotoxicity: none Score = 0

***IN VIVO* STUDIES, Test Article 17-6200-016**

Test	Results
ISO 10993-10 Primary Dermal Irritation	Negligible Irritant PII = 0 (SAL, SO)
ISO 10993-10 Guinea Pig Maximization Test	Nonsensitizer Grade = 0 (SAL, SO)

The finger flange reported in reg-info-cs-03

Studies results summary for TA 13T_58642 (b) (4) finger flange): qualification of the (b) (4) finger flange.

***IN VITRO* STUDIES, Test Article 13T_58642**

Test	Results
ISO 10993-5 Cell Cytotoxicity Elution Test	Cytotoxicity: none Score = 0

***IN VIVO* STUDIES, Test Article 13T_58642**

Test	Results
ISO 10993-10 Intracutaneous Reactivity	Negligible Irritant Score = 0 (SAL,SO)
ISO 10993-10 Guinea Pig Maximization Test	Nonsensitizer Score = 0 (SAL, SO)

The response is adequate.

Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

6.1.5. Sterility Evaluation

☐ Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)

☑ Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

6.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: ☐ **Yes** ☐ **No** ☐ **N/A**	**Mid-Cycle Deficiencies:** ☑ **Yes** ☐ **No** ☐ **N/A**	**Final Deficiencies:** ☐ **Yes** ☐ **No** ☐ **N/A**

Reviewer Comments
The sponsor has not conducted testing after simulated shipping that is representative of the Sponsor's distribution channels.
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No

	Date Sent: 10/2/2020	**Date/Sequence Received:** 10/30/2020
Information Request #2	2. You do not provide testing demonstrating the functionality of your prefilled syringe after simulated shipping. Pleaae provide performance data for your essential performance requirements (i.e., breakloose/glide force and dose accuracy) after simulated shipping representative of your distribution channels.	
Sponsor Response	The tralokinumab drug-device combination product was subjected to simulated shipping per ASTM D4169 and functionality testing of the pre-filled syringe was conducted as part of design verification after simulated shipping. A summary of test results was provided in BLA 3.2.R.3.4 Design Verification, Table 5. This information was sent to the FDA on 06 October 2020 as part of LEO Pharma's responses to the Mid-Cycle Communication Agenda received on 01 October 2020. On 08 October 2020, the FDA confirmed that LEO Pharma's response was adequate to address the FDA request.	
Reviewer Comments	The requested testing was provided in 3.2.R.3.4 Design Verification. The Sponsor provided a new simulated shipping protocol and stated that the new protocol is representative of its distribution channels. Data to demonstrate that the device will perform adequately inclided functionality testing of the pre-filled syringe was conducted as part of design verification after simulated shipping. The simated shipping testing is acceptable.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** 12/14/2020	**Date/Sequence Received:** 12/21/2020
Information Request #3	1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons: The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required. Furthermore, the testing should also be performed after aging of the device, dropping of the device, and simulated shipping. This confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download	
Sponsor Response	(Series 0022)LEO Pharma's response to the information request is included in module 1.11.1. The following new module 3.2.R documents were added to the eCTD: • 3.2.R.3.4.7 Executive Summary safety Claim (b) (4) Needle Guard • 3.2.R.3.4.7 Summary FDA ISO 23908 (b) (4) 510k • 3.2.R.3.4.7 Quality Statement ISO 23908 (b) (4)	

	Summary of FDA Guidance/ISO 23908 Bench Testing Filed in (b) (4) needle guards 510(K)s In 100% of the 512 tested (b) (4) devices the guard completely covered the needle and the lock-out feature was 100% effective; therefore, zero failure was recorded in the present study. The acceptance criteria from the ISO 239081 and FDA guidance2 on sharps injury prevention feature (i.e. zero device failures out of 500 devices activation) was met.
Reviewer Comments	The sponsor provided documentation of the testing of the (b) (4) which was approved through 510(K). This testing is provided, however, the testing does not appear to include any testing with aging of the device (Shelf-Life), dropping of the device, and simulated shipping. It is not clear if the testing is the final manufactured design of the proposed device.
Response Adequate:	☐ **Yes** ☑ **No, See CR #1**

Device	Submission Type	510(K)	510(K) Clearance Date	Stimulated Clinical Use Testing Filed with FDA (510(k) Reference Section)
(b) (4) needle guard	Traditional 510k	(b) (4)	5/29/2001	As per FDA Draft Supplementary Guidance on the *Content of Premarket Notification {510(k)} Submissions for Medical Devices with Sharps Injury Prevention Features*, March 1995, each of the specified acceptance criteria in the controlled simulated clinical use test were either met or exceeded. Stimulated clinical trials were based on predicative devices (b) (4) series. (b) (4)
(b) (4) {Expansion of Indications for Use}	Traditional 510k		4/28/2006	No additional sharps injury prevention testing required for this premarket notification.
(b) (4) needle guard {New Materials for Plunger Rod}	Special 510k		9/20/2012	As per FDA Guidance *Medical Devices with Sharps Injury Prevention Features*, "If your sharps injury prevention feature is currently legally marketed as a part of another device, you may identify that device in lieu of performing simulated clinical use testing." SSI relies on the clinical use studies completed for the legally marketed devices as well as additional simulated use study for the addition of the various plungers. As per FDA guidance and ISO 23908, 168 devices were tested with zero failures. (b) (4)
(b) (4) (b) (4) needle guard {New Design} (b) (4)	Traditional 510k		3/26/2013	As per FDA Guidance *Medical Devices with Sharps Injury Prevention Features*, 500 devices were tested with zero failures for a *"97.5% confident that the true failure rate was no higher than 0.7% and 99.5% confidence that it is no higher than 1.1%"*. (b) (4)

Follow-On Deficiency	**Date Sent: 1/15/2021**	**Date/Sequence Received: 1/22/2021**
Information Request #3	You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons: The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required. Furthermore, the testing should also be performed after aging of the device, dropping of the device, and simulated shipping. This confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download	

Additional Sponsor Response in Late-Cycle Briefing Package	(Series 0026) *In the Background Package, the Agency cited the 2005 CDRH Guidance for Medical Devices with Sharps Injury Prevention Features as a source of the request to perform testing to a confidence and reliability interval of 95%/99%. This Guidance recommends evaluating 500 devices in a simulated clinical use study to demonstrate sharps injury prevention performance with a 95% confidence interval and 99% reliability. This Guidance does not refer to design verification nor preconditioning and drop testing. Therefore, LEO Pharma does not consider this Guidance applicable to the confidence and reliability parameters for design verification/functional testing of the safety features.* *Furthermore, the Guidance states: "If your sharps injury prevention feature is currently legally marketed as a part of another device, you may identify that device in lieu of performing simulated clinical use testing". The* (b) (4) *LEO Pharma has clinical experience with the tralokinumab combination product for the treatment of atopic dermatitis with 3 complaints involving 4 devices with needle safety device deployment failure out of 226,139 devices used, as described in the 21 December 2020 response to an information request (Sequence 0022). This provides additional evidence for the safe use of the needle safety device in a representative clinical environment.* *LEO Pharma agrees that design verification testing of the needle safety performance of the final finished combination product is required. Data to support the needle safety performance and reliability of the combination product has been provided in the BLA (refer to M3.2.R.3.4), and in the 21 December 2020 response. The combination product test articles used for Design Verification testing were produced by the representative manufacturing pro- cess and following preconditioning including real-time aging, drop testing according to ISO 11608-1, and shipping simulation according to ASTM 4169-16. The preconditioning was per- formed individually as is standard practice for design verification testing and described in the recognized international standards for testing of needle-based injection systems. The request for sequential preconditioning by the Agency is beyond the requirements of any regulatory guidance or medical device standard known to LEO Pharma.* *Selection of confidence intervals and reliability values for design verification of the tralokinumab combination product was done in accordance with risk-based sampling criteria which consider the potential impact to the user if the feature does not perform as intended. This ap- proach has traditionally been accepted by the Agency for a range of combination products in clinical trials and in marketing applications and resulted in the sample sizes shown in the LEO Pharma communication of 21 December 2020. The sample sizes were also included in the original BLA (refer to M3.2.R.3.4).* *In conclusion, the safety and reliability of the* (b) (4) *has been demonstrated based on the design verification performed for the tralokinumab combination product, extensive use of the* (b) (4) *for other legally mar- keted products and further supported by the complaint data from the Tralokinumab clinical study. LEO Pharma respectfully requests that the Agency reconsider its position on this sub- stantive review issue.*

Reviewer Comments	The sponsor provided documentation of the testing of the (b) (4) which was approved through 510(K) (As referenced for sequence 0022). This was provided in response to IR#3. This testing is provided, however, the testing did not include any testing with aging of the device (Shelf-Life), dropping of the device, and simulated shipping. The sponsor references section 10 of the guidance, p. 10, under Simulated Clinical Use Testing, where it says "For devices that include sharps injury prevention features, we recommend that you conduct simulated clinical use testing and provide an analysis of the results from simulated clinical use testing and a summary of the results and conclusions. *If your sharps injury prevention feature is currently legally marketed as a part of another device, you may identify that device in lieu of performing simulated clinical use testing.*" However, the referenced guidance is specifically for 510(k) submissions. Eventhough the argument is for 510k cleared devices, they cannot leverage this data because of differences in design/mfg/handling of those products compared to theirs. They didn't provide a comparison of performance. In their response, "LEO Pharma agrees that design verification testing of the needle safety performance of the final finished combination product is required" They had provided the sample size. The additional preconditioning we are requesting is representative of intended use. Their sampling is unacceptable as we explained. The agency determine a reliability of 99% is appropriate for needle safety in general because of the severity of the risk with needle stick (HIGH). A reliability of 90% and 97.5% is not acceptable and would deviate from how we evaluate other submissions.
Response Adequate:	☐ **Yes** ☑ **No, See CR #1 Sent on 4/23/2021**

Response to CR

	Date Sent: **4/23/2021**	**Date/Sequence Received:** **7/2/2021**
Complete Response #1	You provided a response to an information request dated, December 14, 2020, which provided documentation of (b) (4) testing of the (b) (4) associated 510(k) references to address our request for data verifying the needle safety performance of your combination product at an appropriate reliability limit (95% confidence /99% reliability) and pre-conditioning (aging, drop testing and shipping). While the testing provided evidence for performance of the 510(k) cleared needle safety device component, the testing did not include testing of your final finished combination product or testing after the requested representative preconditioning (aging of the device, dropping of the device, and simulated shipping). You also provided additional information in your Late-Cycle background package dated January 22, 2021, where you asserted that The (b) (4) is a 510(k) FDA cleared medical device that is manufactured (b) (4) • This device has been cleared by the FDA to provide protection from accidental needle stick injury. • It has been commercially marketed worldwide since 2001 with numerous products.	

	• A study evaluating the (b) (4) device is summarized in the attached document from (b) (4) demonstrating 512 successful device safety feature activation with 0 failures. Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, design differences between your final finished combination product and currently marketed products, combination product manufacturing and preconditioning would impact the performance and reliability. Failure of the needle safety device to perform adequately may result in serious risks (accidental contaminated needle sticks). Provide testing demonstrating that your final finished combination product needle safety performance (needle safety activation and lockout) can meet a confidence and reliability of 95%/99% after aging of the device to the proposed shelf-life, drop testing and simulated shipping per ASTM 4169-16 *Standard Practice for Performance Testing of Shipping Containers and Systems* sequentially. The recommended confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download.
Sponsor Response	Based on the email communication of June 7, 2021 and agreements at the Type A teleconference of June 9, 2021, LEO Pharma is providing testing results for the accessorized pre-filled syringe (APFS) needle safety performance using final finished product after preconditioning over the proposed shelf-life of (b) (4) month to the appropriate confidence and reliability of 95%/99%. The response is found in Series 0041, 3.2.R 10 Technical Assessment os Needle Safety Performance: The scope of this report includes safety feature activation testing for Tralokinumab APFS 2x 150mg/mL. The functional testing was performed after (b) (4) months of real time aging followed by drop and simulated shipping conditioning per ASTM D4169-16. Needle safety performance is demonstrated by Needle Safety Activation (confirmation of lockout as attribute data) and testing of Compressive Override Force after injection (as variable data). Samples representing the final finished combination product were placed in commercially representative shipper cases and were conditioned in accordance with relevant sections of ASTM D4169-16 procedures for drop and vibration conditioning prior to testing. To most accurately simulate actual use of the device, Needle Safety Activation was confirmed by manual operation with six operators after they expelled into a waste container. Needle Safety Compressive Override Force measurements were performed using mechanical force tester. The sample size for variable testing (Compressive Override Force) was determined based on statistical techniques and ISO 11608-1, Annex-B (one sided tolerance limit factors). For attribute data (confirmation of lockout), a reliability approach was used to determine the sample size based on ISO 16269-6. Data for the attribute testing are analyzed as "pass/fail".

Table 1 **Statistical Sampling Plan**

Functional Requirement	Date Type (Attribute/Variable)	Confidence Level	Reliability	Minimum Sample Size
Needle Safety Activation (lockout confirmation)	Attribute	95%	99%	299
Needle Safety Compressive Override Force	Variable	95%	99%	29

Table 2 **Summary of Needle Safety Performance after Preconditioning**

Requirement name	Product requirement	Acceptance criteria	Data summary	Passed/ Not passed
Needle Safety Activation (lockout confirmation)	The combination product needle safety feature shall activate (lockout) when the injection stroke has been completed	Accept on 0 failures. Reject on 1 or more failures	n = 300 pass = 300 fail = 0	Pass
Needle Safety Compressive Override Force after injection	After dosing, the combination product needle safety lockout feature shall have a compressive override force of (b) (4)	Accept on 95%C/99%R tolerance interval, F (b) (4) (b) (4) for tested sample size)	n = 30 Lower Tolerance Limit = (b) (4) k_{actual} = 14.84	Pass

Additional information on the testing can be found in the technical reports in section 3.2.R.3.4.16 Needle Safety Feature Activation Following (b) (4) Months Shelf Life and Simulated Shipping (Needle Safety Activation testing) and 3.2.R.3.4.8 Needle Safety Feature testing, tralokinumab 1 ml APFS (needle safety Compressive Override Force). *(provided in Series 0033)*

To extend the shelf-life to 36 months, an accelerated aging study will be performed. The needle safety performance of the final, finished tralokinumab APFS 2x 150mg/1mL will be evaluated after accelerated aging time equivalent to 36 months shelf-life and simulated shipping per ASTM D4169-16. Accelerated aging duration is based on ASTM F1980 with a reaction rate coefficient (Q10) of 2, samples will be stored at 40°C for 97 days which is equivalent to 36 months (1,095 days) of real-time aging at 5°C. The protocol for accelerated aging is provided in section 3.2.R.3.4.17 Needle Safety Performance Following 36 Month Accelerated Aging. These samples will be subjected to the identical preconditions and test methods described in 3.2.R.3.4.12. These accelerated data will support a shelf-life extension to 36-months and will be implemented upon its availability.

Reviewer Comments

The sponsor has provided EPR data for Needle Safety Activation and needle safety Compressive Override Force with confidence and reliability of 95%/99%. The functional testing was performed after 24 months of real time aging followed by drop and simulated shipping conditioning per ASTM D4169-16.

The results show no failures for Needle Safety Activation and accewptable Compressive Override Forc (b) (4)

The results are acceptable.

	Note: The protocol for accelerated aging is provided in section 3.2.R.3.4.17 Needle Safety Performance Following 36 Month Accelerated Aging is provided, however, the data is not provided. Ths would require an amendment. The current shelf life is 24 months.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

7. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	The combination product shall deliver a dose volume (b) (4) mL	Y
Break loose Force	Maximum break loose force (b) (4)	Y
Glide Force	Maximum glide force (b) (4)	Y
Cap Removal Force	N/A	N/A
Rigid need;e shield pull-off force	The combination product shall have a rigid needle shield pull-off force that is (b) (4)	Y

Reviewer Comments

The Sponsor has included the EPRs of the device constituent parts of the combination product in the release testing of the device. This is an acceptable control strategy. The needle safety activation was notadequately evaluated. An IR was sent on December 14, 2020, however, the sponsor presented a resppnse based on prior approval of the device through the 510(k) process, however, testing for shelf-life and shipping is needed with the current PFS product. A major deficiency is recommended.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

7.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION		
Filing Deficiencies:	**Mid-Cycle Deficiencies:**	**Final Deficiencies:**

☐ Yes ☐ No ☐ N/A	☑ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

The sponsor provided an adequate device desciption for the Pre-Filled Syringe prefilled (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function. The sponsor had conducted performance testing of the device demonstrating that the device met Essential Performance Requirements for validation, after simulated shipping, and aging(shelf-life). While the sponsor provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. The testing is not adequate mostly for sample size and reliability of the needle safety feature which is essential for preventing accidental needle sticks.

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Filing/74-Day Information Requests

8.2. Mid-Cycle Information Requests

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

1. For the extended finger flange, needle safety guard, and plunger rod, which are intact skin contacting, you provide Cytotoxicity and Skin sensitization testing, that you indicate conforms to the criterion of ISO 10993, however you do not provide reports to verify that conformance. Furthermore, per FDA guidance *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"* the appropriate endpoints based on your contact classification are: Cytotoxicity, Sensitization, and Irritation. Therefore, please provide testing reports for cytotoxicity, sensitization, and irritation for the extended finger flange, needle safety guard and plunger rod.
2. You do not provide testing demonstrating the functionality of your prefilled syringe after simulated shipping. Pleaae provide performance data for your essential performance requirements (i.e., breakloose/glide force and dose accuracy) after simulated shipping representative of your distribution channels.

8.3. Interactive Information Requests

8.3.1. Interactive Information Requests sent on 12/14/2020

1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons:

   The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required.

   Furthermore, the testing should also be performed after aging of the device, dropping of the device, and simulated shipping.

   This confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download

Clinical Inspection Summary

Date	2/25/21
From	Christian Shenouda, MD Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Strother Dixon, Regulatory Project Manager Hamid Tabatabai, M.D., Clinical Reviewer David Kettl, M.D., Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
NDA	BLA 761180
Applicant	LEO Pharma, Inc.
Drug	Tralokinumab
NME	Yes
Proposed Indication(s)	Atopic Dermatitis
Consultation Request Date	5/29/2020
Summary Goal Date	2/27/2021
Action Goal Date	4/13/2021
PDUFA Date	4/27/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Andrew Alexis, Lawrence Parish, and Tien Nguyen were inspected in support of this BLA covering Protocols LP0162-1326, LP0162-1325 and LP0162-1339. Dr. Parish's site had been terminated by the sponsor during the trial for non-compliance. Due to concerns related to study conduct, potential unblinding, and data integrity and reliability noted during the inspection of Dr. Parish's site (in particular with regard to the Week 16 EASI scores), we recommend a sensivity analysis be conducted with regard to the data from this site.This was the only site inspected for Protocol LP0162-1326. Based on the results of Drs. Andrew Alexis and Tien Nguyen inspections, the studies LP0162-1325 and LP0162-1339 appear to have been conducted adequately, and the data generated by these sites appears acceptable in support of the respective indication.

II. BACKGROUND

Atopic Dermatitis (AD) is a common inflammatory skin disease manifested by intense itch, eczematous skin lesions, and potential impact on quality of life. Tralokinumab is a monoclonal antibody that specifically binds to the cytokine interleukin-13 (IL-13) receptor and inhibits IL-13 signaling. Tralokinumab is intended for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

The sponsor submitted this BLA application with data from 3 pivotal trials for which the review team requested clinical inspections. The trials shared the same design, including inclusion and exclusion criteria, primary endpoints, and timepoints for assessment of efficacy. A summary of the three trials is presented below, and specific differences are noted in sections related to the trials themselves.

All three protocols were phase 3, international, multi-site, randomized, double-blind, placebo-controlled trials. They consisted of a screening period of 2 to 6 weeks (Weeks -6/-2 to 0), an initial treatment period of 16 weeks (Weeks 0 to 16), and a maintenance treatment period (either 16 or 36 weeks).

Protocols LP0162-1325 and LP0162-1326 involved the study medication tralokinumab vs. placebo, whereas LP0162-1339used a topical corticosteroid (TCS) with either the study medication or placebo.

All subjects were instructed to use emollient at least twice daily during the screening period and to continue this treatment throughout the trial. A loading dose of the study medication or placebo was given on Day 0, and a maintenance dose was given every 2 weeks thereafter. At 16 weeks, the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) were assessed. Subjects with a clinical response could enter a maintenance treatment phase where they were re-randomized in a blinded fashion to either tralokinumab every 2 weeks or tralokinumab every 4 weeks.

Pertinent inclusion and exclusion criteria (for all studies):

- Inclusion Criteria: Adults with a diagnosis of atopic dermatitis for >1 year without adequate response to topical medications, ≥10% body surface area (BSA) at screening and baseline, EASI of ≥12 at screening and ≥16 at baseline, IGA score of ≥3 at screening and at baseline, and Worst Daily Pruritus numeric rating scale (NRS) average score of ≥4
- Exclusion Criteria: Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomization, use of tanning bed or phototherapy 6 weeks prior to randomization, use of topical corticosteroid or calcineurin inhibitor 2 weeks prior to randomization, and active skin infection within one week of randomization.

Actual inclusion/exclusion criteria were more extensive than listed in this summary. Please refer to the protocols for more detail.

The *co-primary efficacy endpoint* consisted of the percentage of subjects achieving a clinical response at Week 16 (defined as IGA of 0 or 1 on a 5-point scale ranging from 0 [clear] to 4 [severe] or at least a 75% reduction in Eczema Area and Severity Index [EASI] score from baseline [EASI75]). The IGA and EASI were assessed every 2 weeks during the trial, but the primary endpoint focused on the outcome at 16 weeks.

III. PROTOCOLS

LP0162-1325

Title: "A randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab monotherapy in subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy" (ECZTRA 1)

Subjects: 802 subjects (603 Tralokinumab/199 placebo) enrolled at 112 US and international sites (Germany, France, Spain and Japan)

Study Initiation and Completion Dates: May 30, 2017 to July 18, 2019

Randomization Scheme: Enrolled subjects were randomized in a 3:1 ratio to treatment with tralokinumab 300 mg every 2 weeks (Q2W) or placebo. Randomization was stratified by region (Asia, Europe, and North America) and disease severity (Investigator's Global Assessment [IGA] 3 or 4).

LP0162-1326

Title: "A randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab monotherapy in subjects with moderate to severe atopic dermatitis who are candidates for systemic therapy" (ECZTRA 2)

Subjects: 794 subjects (593 Tralokinumab/201 Placebo) enrolled at 107 domestic and international sites (Australia, Canada, Denmark, Italy, Korea, Poland, Russia, and Great Britain)

Study Initiation and Completion Dates: June 29, 2017 to August 14, 2019

Randomization Scheme: Enrolled subjects were randomized in a 3:1 ratio to treatment with tralokinumab 300 mg every 2 weeks (Q2W) or placebo. Randomization was stratified by region (Asia, Australia, Europe, and North America) and disease severity (Investigator's Global Assessment [IGA] 3 or 4).

LP0162-1339

Title: "A randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids in subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy" (ECZTRA 3)

Subjects: 380 subjects (253 Tralokinumab+Topical Corticosteroids [TCS] /127 placebo +TCS) enrolled via 63 domestic and international sites (Belgium, Canada, Germany, Great Britain, Poland, Spain, Netherlands)

Study Initiation and Completion Dates: February 27, 2018 to June 26, 2019

Randomization Scheme: Enrolled subjects were randomized in a 2:1 ratio to treatment with tralokinumab 300 mg+TCS every 2 weeks (Q2W) or placebo+TCS every 2 weeks. Randomization was stratified by region (Europe and North America) and disease severity (Investigator's Global Assessment [IGA] 3 or 4).

Rationale for Site Selection

The following clinical investigator (CI) sites were chosen for inspection using a risk-based approach, including number of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

IV. INSPECTION RESULTS

1. Dr. Tien Nguyen
   Site # 125
   17271 Brookhurst Street
   Fountain Valley, CA 92708
   Inspection Dates: 9/9/2020 to 9/15/2020

   At this site for Protocol LP0162-1325, 23 subjects were screened, 16 were randomized, and 12 subjects completed the study. There were 4 subjects who withdrew from the study (Subjects (b) (6)), and all were assigned to placebo except for Subject (b) (6). Application materials state that all these subjects withdrew consent or were unable to comply with the study schedule; there is no indication that any withdrew due to an adverse event. All of these subjects, however, did make it to the Week 16 primary efficacy endpoint assessment.

   Records reviewed during the inspection included, but not limited to, informed consent, financial disclosures, screening logs, adverse event reporting, primary endpoint data, concomitant medications, IRB approvals, correspondence, training records, and protocol deviations.

   The FDA field investigator reviewed the records of all 16 randomized subjects for verification of the primary efficacy endpoint data. There was only one discrepancy noted. For Subject (b) (6) on the EASI, source records documented a score of 7.6 whereas the data line listing provided by the sponsor indicated a score of 17.6. This subject was assigned to the placebo group, and the sponsor attributed the discrepancy to a data entry error.

   There were no serious adverse events at this site. There was one instance of under-reporting of an adverse event. In this instance, Subject (b) (6), who was assigned to

tralokinumab, had a second-degree sunburn that was not reported.

In addition, Subject (b) (6), who whas assigned to tralokinumab, was prescribed a Medrol dose pack after a trip to the emergency room for flu-like symptoms. This occurred after the week 16 EASI and IGA were performed, and the event was recorded as an adverse event by the site. Systemic corticosteroids are listed as a prohibited medication. The medication was documented on the concomitant medication record, and the CI reported this medication to the sponsor. However, this protocol deviation was not in the data line listings provided by the sponsor.

2. Dr. Jean-Philippe Lacour
Site # 273 of Study LP0162-1325
Hôpital de l'Archet II
Service de Dermatologie-Vénérologie
151, Route Saint Antoine de Ginestière
Nice, Alpes-Maritimes 6202
France

The COVID-19 global pandemic has significantly limited OSI's ability to conduct on-site Good Clinical Practice (GCP) inspections, especially international inspections. As a result, and to protect the health, safety, and welfare of FDA employees and study staff, the need for this inspection in support of BLA 761180 was re-evaluated. Following discussions between OSI and the review division, a decision was made that assessment of the application could proceed without this GCP inspection.

3. Dr. Lawrence Parish
Site #423
1760 Market Street, Suite 301
Philadelphia, PA 19103
Inspection Dates: 8/31/2020 – 9/11/2020

At this site for Protocol LP0162-1326, 25 subjects were screened, and 20 subjects were enrolled and randomized. This site was terminated for non-compliance by the sponsor during the trial, at which time 14 subjects had completed the Week 16 assessments. Of note, OSI had not been informed that this site had been terminated at the time of the site selection meeting and issuance of the assignment memo.

Records reviewed during the inspection included, but not limited to, FDA Form 1572 documentation, training, delegation of authority, informed consent, subject eligibility, efficacy endpoint data, adverse events, monitoring reports, IRB approvals and correspondence, record retention policy, and investigational product accountability (receipt, storage, administration, and disposition records).

The primary efficacy endpoint data (EASI and IGA) for all 14 subjects who completed the

Week 16 assessments before the site was terminated by the sponsor were veriried; no discrepancies were noted. However, review of the source data for these endpoints showed that the clinical investigator used a scribe (his study coordinator, who would never sign) to record EASI scores, and this (and other documentation) frequently lacked CI signatures, initials and/or dates, or this information was placed up to two weeks after the assessment was performed. The inspection also noted multiple out of window visits.

A potential blinding issue was also noted. The blinded study coordinator was often in the room during administration of the IP, as his initials were on an "IMP Handling" study form. This could have resulted in him having knowledge of the subject's group assignment given the fact that the active drug and placebo were visually distinct.

There were no SAEs reported at the site. Also, there was no evidence of underreporting of adverse events. However, site monitoring reports documented that several adverse event entries were missing dates and signatures.

Reviewer's comment: Due to the record-keeping issues noted during the inspection (in particular with regard to the Week 16 EASI scores) as well as concerns regarding data integrity and reliability as well as potential unblinding, we recommend a sensivity analysis be conducted with regard to the data from this site.

4. Dr. Andrew Alexis
Site # 810
2109 Broadway, 2nd Floor;
New York, NY 10023
Inspection Dates: 10/26/2020 to 10/29/2020

At this site for Protocol LP0162-1339, 20 subjects were screened, 13 subjects were enrolled and randomized, and 10 subjects completed the protocol. Of the three subjects who did not complete the study, one subject assigned to placebo (Subject (b) (6)) withdrew consent due to scheduling issues. Two subjects assigned to tralokinumab (Subjects #s (b) (6)) withdrew due to an injection site reaction.

Records reviewed during the inspection included, but were not limited to, informed consent, eligibility, protocol adherence, adverse event (AE) reporting, delegation of authority, financial disclosure, institutional review board (IRB) approvals, training logs, notes to file and investigational product accountability/handling.

The primary efficacy endpoint data were verified for all 13 randomized subjects; no discrepancies were noted. There were no SAEs reported at this site, and there was no evidence of under-reporting of adverse events.

{See appended electronic signature page}

Christian N. Shenouda, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm. BLA 761180
DDDP Review Division /Division Director/Kendall Marcus
DDDP Review Division /Medical Team Leader/ David Kettl
DDDP Review Division /Project Manager/ Strother Dixon
DDDP Review Division/MO/ Hamid Tabatabai
OSI/Office Director/ Ni Khin
OSI/DCCE/ Division Director/ David Burrow
OSI/DCCE/Branch Chief/ Kassa Ayalew
OSI/DCCE/Team Leader/ Phillip Kronstein
OSI/DCCE/GCP Reviewer/ Christian Shenouda
OSI/ GCP Program Analysts/ Yolanda Patague
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTIAN N SHENOUDA
02/25/2021 09:26:53 AM

PHILLIP D KRONSTEIN
02/25/2021 09:46:21 AM

KASSA AYALEW
02/25/2021 09:49:15 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 24, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761180
Product Name and Strength:	(b) (4) (tralokinumab-ldrm) injection, 150 mg/mL
Applicant/Sponsor Name:	Leo Pharmaceuticals
OSE RCM #:	2020-883-3 and 2020-885-3
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader (acting):	Ebony Whaley, PharmD, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling, Prescribing Information (PI), Instructions for Use (IFU), and Patient Package Insert (PPI) on February 22, 2021 for Adtralza. The Division of Dermatology and Dentistry (DDD) requested that we review the revised carton labeling, PI, IFU, and PPI, for (b) (4) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

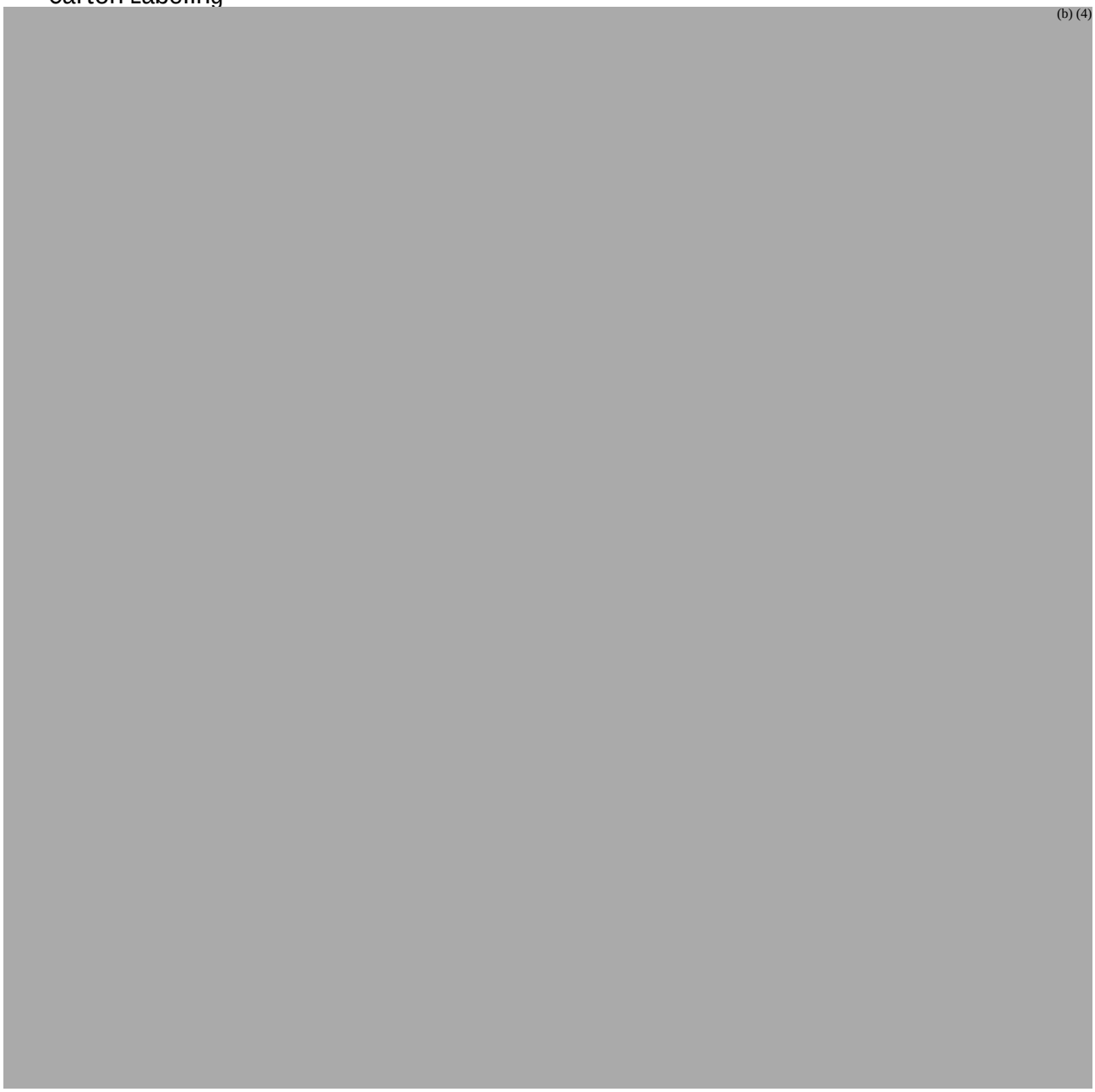
2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel M. Label and Labeling Review MEMO for (b) (4) (BLA 761180). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 10. RCM No.: 2020-883-2 and 2020-885-2.

APPENDIX A. IMAGES OF LABELING RECEIVED ON FEBRUARY 22, 2021

Carton Labeling



Prescribing Information (Image not shown)
\\CDSESUB1\evsprod\bla761180\0031\m1\us\annotated-draft-labeling-text-uspi.pdf

Instructions for Use (Image not shown)
\\CDSESUB1\evsprod\bla761180\0031\m1\us\annotated-draft-labeling-text-ifu.pdf

Patient Package Insert (Image not shown)
\\CDSESUB1\evsprod\bla761180\0031\m1\us\annotated-draft-labeling-text-ppi.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
02/24/2021 02:04:19 PM

EBONY A WHALEY
02/24/2021 04:12:21 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 10, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761180
Product Name and Strength:	(b) (4) (tralokinumab-ldrm) injection, 150 mg/mL
Applicant/Sponsor Name:	Leo Pharmaceuticals
OSE RCM #:	2020-883-2 and 2020-885-2
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling, Instructions for Use (IFU) and Patient Package Insert (PPI) on February 1, 2021 and revised container labels and carton labeling on February 9, 2021 for (b) (4) Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels, carton labeling, IFU and PPI, for (b) (4) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[a]

2 DISCUSSION

We provide our recommendation from our previous reviews,[a,b] the Applicant's response, and our analysis of the Applicant's response in the table below.

[a] Schlick J, Patel M. Label and Labeling Review for (b) (4) (BLA 761180). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 21. RCM No.: 2020-883 and 2020-885.
[b] Patel M. Label and Labeling Review MEMO for (b) (4) (BLA 761180). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 21. RCM No.: 2020-883-1 and 2020-885-1.

Identified Issues and Recommendations History				
Identified Issue	Rationale for Concern	Agency's Recommendation	Applicant's Response submitted February 1, 2021	Agency's Analysis of Applicant's response
Product Design				
The human factors validation study identified use errors with the critical task of giving a second syringe to complete the full 300 mg dose.	Based on your use-related risk analysis (URRA), the harm to a patient of not injecting the second syringe to complete a full dose results in an incomplete dose and affects efficacy if the error occurs multiple	Consider packaging the 2 syringes together within the carton (for example in a sleeve) to minimize the risk of users only administering one syringe. Additionally, consider including a statement on the sleeve, "Administer both syringes to get your full prescribed dose" using bold font, color, or some other means to ensure the statement is prominent.	Based on the rationale provided below, packaging the 2 syringes together within the carton in a sleeve is not considered necessary since testing results support the current configuration of instructions for use and packaging material as sufficient to minimize the risk of medication error due to incomplete dosing (*LEO Pharma would appreciate prompt FDA feedback on our rationale not to consider a sleeve in the carton*). LEO Pharma proposes to highlight the current text inside the lid under the "repeat" symbol "For a 300 mg dose, two 150 mg syringes are required. Inject one syringe after the other." in plum color (see attachment). This is to further ensure that this information is seen and understood by the user. Rationale: LEO Pharma has designed a carton	We find the Applicant's proposed revision to highlight the current text inside the carton lid under the "repeat" symbol "For a 300 mg dose, two 150 mg syringes are required. Inject one syringe after the other." in plum color acceptable. Thus, we have no further recommendations at this time. (See carton labeling image in Appendix A).

	times.		containing two accessorized prefilled syringes (APFS) - 150 mg/mL x 2 configuration, which has been through extensive development and testing to ensure a design which will provide adequate and robust protection to the combination product and a design which can be handled and used as intended by the intended user population. The development of the design included identification of use risks and mitigation through the risk management process and iterative human factors studies. Furthermore, design verification testing including simulated shipping and human factors validation has been performed on the final commercial design. LEO Pharma believes that (b) (4) can be safely self-administered and that the instructions for use and carton (150 mg/mL x 2 configuration) provide sufficient information for the user to minimize the risk of medication error due to incomplete dosing. This has been demonstrated in a human factors summative study (reference to M3.2.R.3.6) which was performed to validate the design and use of the APFS, instructions for use and the carton (150 mg/mL x 2 configuration). The human factors validation study included 21	

			subjects who were trained in using the APFS and 45 subjects who were not trained. All of them received the carton containing two syringes and the instructions for use. All of the 21 trained subjects successfully injected 2 simulated injections without user errors, close calls, or difficulties. All trained subjects understood that two syringes were needed for a full dose. 40 of the 45 untrained subjects successfully completed 2 simulated injections to complete a full dose and understood that two syringes were needed for the full dose. For four of the participants, the reason for not completing the two injections was that subjects did not engage with the IFU. When prompted to engage with the IFU, they reported that they thought the information was clear. The fifth participant assumed that two syringes was an adult dose and asked to see the prescription label, the participant self-corrected and understood two injections were needed. While a few subjects failed to inject both syringes to constitute a full dose, untrained users in the real world would have the benefit of a prescription label and a conversation with their prescribing	

			and dispensing healthcare provider regarding dosing. Furthermore, it is expected that the healthcare provider would provide training before prescribing for home use as stated in the USPI: (b) (4) *is intended for use under the guidance of a healthcare provider. A patient may self-inject* (b) (4) *after training in subcutaneous injection technique*".	
Instructions for Use (IFU)				
The statement in Step 4 of the IFU does not include an introductory statement to delineate what to do if the dose is 600 mg or 300 mg. Additionally, the heading for Step 4 does not describe the 4 syringes needed to complete the 600 mg initial dose.	This lack of clarity could cause confusion with use of the product, resulting in an underdose.	Revise the heading of Step 4 (b) (4) to, "Injecting the next syringe." -- Additionally, revise the statement, (b) (4) (b) (4) (b) (4) to read, • "To get your full prescribed initial dose of **600 mg**, you will need to give 4 injections." • "To get your full prescribed dose of **300 mg**, you will need to	LEO Pharma accepts this. The text has been revised accordingly in the IFU. -- The intention with the information in the IFU is to instruct the patient on how to inject the maintenance dose on 300 mg which is what is provided in one carton (150mg/mL x 2 syringe configuration). LEO Pharma finds it more appropriate to include the FDA proposed text (with slight modifications) into the PPI instead of into the IFU. The following underlined text has been added in the PPI under the section entitled, "How should I use (b) (4) under the bullet:	-- After considering the Applicant's rationale, we maintain our recommendation to include the information on how to achieve a 600 mg dose in the IFU since the same intended user will use the same carton configuration and IFU to administer the initial dose of 600 mg as well as the maintenance dose of

		give 2 injections." Additionally, revise the Note statement from, (b) (4) (b) (4) to read, "Make sure you give your next injection within the same body area, but at least 1 inch (3 cm) away from where you injected (b) (4) in Step 3."	• Use (b) (4) exactly as prescribed by your healthcare provider. o (b) (4) comes as a single-dose (150 mg) prefilled syringe with needle guard. (b) (4)	300 mg. We provide a recommendation to the Applicant below. We defer to the Patient Labeling Team (PLT) on whether to also include this information in the PPI.

3 CONCLUSION

We find the revised container labels and carton labeling acceptable from a medication error perspective. We also find the Applicant's proposal to highlight the statement regarding the number of syringes to administer a full dose on the carton flap acceptable from a medication error perspective. However, the revised statement in the IFU related to the prescribed dose is unacceptable from a medication error perspective because it may result in confusion leading to underdose medication error. We provide a recommendation for the Applicant below.

4 RECOMMENDATIONS FOR LEO PHARMACEUTICALS

We recommend the following be implemented prior to approval of this BLA:

A. Instructions for Use (IFU)

a. We maintain our previous recommendation to quantify the dose in the Instructions for Use (IFU) for clarity since the carton configuration can be used for the initial dose of 600 mg as well as the maintenance dose of 300 mg. Revise the statement, (b) (4) (b) (4) to read,

"To get your full prescribed dose, you will need to give more than 1 injection."

- "To get your full prescribed initial dose of 600 mg, you will need to give 4 injections."
- "To get your full prescribed dose of 300 mg, you will need to give 2 injections."

6 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
02/10/2021 03:53:32 PM

MILLIE B SHAH
02/10/2021 03:58:10 PM

LOLITA G WHITE
02/11/2021 12:47:17 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	2/4/2021		
To:	Strother Dixon		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	Other
From	Stephen M. Retta OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C GHDB		
Subject	BLA 761180, (b) (4) (Tralokinumab) ICC2000441		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 2/4/2021 ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☑ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761180
Sponsor	Leo Pharma Inc.
Drug/Biologic	(b) (4) (b) (4) (Tralokinumab)
Indications for Use	is proposed for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately contolled with topical prescription therapies or when those therapies are not advisable.
Device Constituent	Pre-Filled Syringe
Related Files	BLA 761180

Important Dates	
Filing	June 11, 2020
74-Day Letter	June 22, 2020
Midcycle Meeting/IRs due	September 25, 2020
Final Lead Device Review Memo Due	December 18, 2020
PDUFA Date	November 13, 2020

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☑ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☑ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

1. You provided a response to an information request dated, December 14, 2020, which provided documentation of (b) (4) (b) (4) associated 510(k) references to address our request for data verifying the needle safety performance of your combination product at an appropriate reliability limit

(95% confidence /99% reliability) and pre-conditioning (aging, drop testing and shipping). While the testing provided evidence for performance of the 510(k) cleared needle safety device component, the testing did not include testing of your final finished combination product or testing after the requested representative preconditioning (aging of the device, dropping of the device, and simulated shipping). You also provided additional information in your Late-Cycle background package dated January 22, 2021, where you asserted that The (b) (4) is a 510(k) FDA cleared medical device that is manufactured (b) (4)

- This device has been cleared by the FDA to provide protection from accidental needle stick injury.
- It has been commercially marketed worldwide since 2001 with numerous products.
- A study evaluating the (b) (4) device is summarized in the attached document from (b) (4) demonstrating 512 successful device safety feature activation with 0 failures.

Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, design differences between your final finished combination product and currently marketed products, combination product manufacturing and preconditioning would impact the performance and reliability. Failure of the needle safety device to perform adequately may result in serious risks (accidental contaminated needle sticks). Provide testing demonstrating that your final finished combination product needle safety performance (needle safety activation and lockout) can meet a confidence and reliability of 95%/99% after aging of the device to the proposed shelf-life, drop testing and simulated shipping per ASTM 4169-16 *Standard Practice for Performance Testing of Shipping Containers and Systems* sequentially.

The recommended confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download.

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

3. PURPOSE/BACKGROUND

3.1. Scope

Leo Pharma Inc. is requesting approval of a prefilled syringe (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The device constituent of the combination product is a Pre-Filled Syringe.

Choose an item. has requested the following consult for review of the device constituent of the combination product:

Please review the device component of this original BLA submission.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

☒ Device performance
☒ Biocompatibility of the patient contacting components
☐ Sterility
☒ Stability – device performance on stability
☒ Essential Performance Requirements (EPR) Control strategy
☐ Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
(b) (4) (Tralokinumab)	The APFS is intended to deliver a 1 mL injection of tralokinumab via subcutaneous delivery to patients with moderate to severe atopic dermatitis (AD).
Pre-Filled Syringe	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	3.2.R
0001	3.2.P
0022	3.2.R.3.4.7

4. DEVICE DESCRIPTION

4.1. Device Description

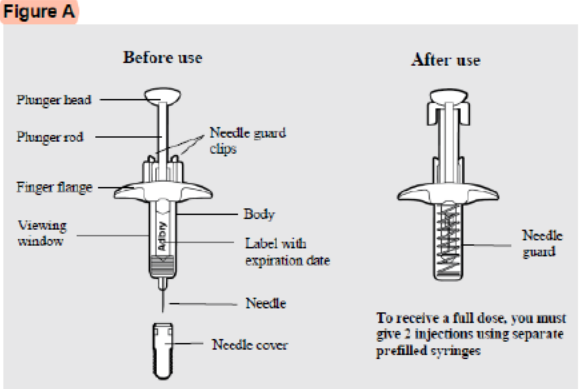
From 3.2.R.3 reg-info-device-discription. The combination product consists of an **accessorized prefilled syringe** (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab.

One intended user population includes HCPs administering tralokinumab to patients in a clinical use environment. A second intended user population includes patients performing self-administration and caregivers performing third party administration to patients. It is intended that patients and caregivers will use th APFS in a non-clinical environment, most commonly at home.

The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function. It is designed to administer a 1 mL fixed dose of 150 mg/mL tralokinumab, 2 × 1 mL APFS provides one full 300 mg dose. The APFS is supplied pre-assembled and ready for use.

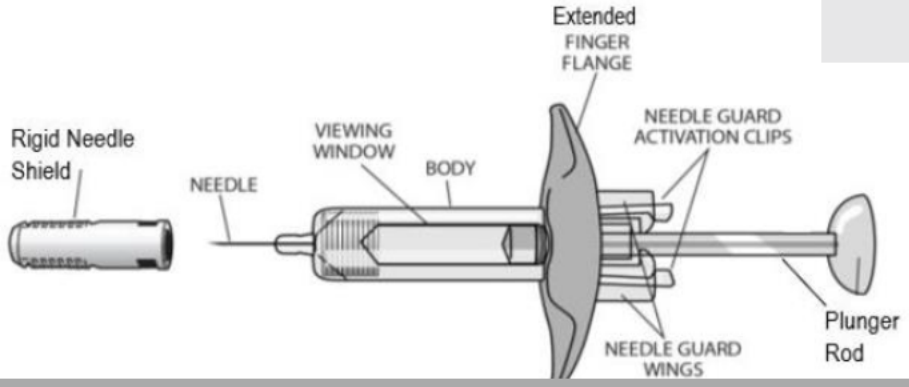
The APFS consists of a prefilled syringe sub-assembly (PFS-SA) consisting of a 1 mL long syringe barrel with a ½ inch **27 gauge** (b) (4) **needle**, rigid needle shield(RNS) and plunger stopper. The accessorized part consists of a needle safety guard, plunger rod and extended finger flange. The needle safety guard is composed of a needle guard body with activation clips and wings.

Figure A



The prefilled syringe is (b) (4) in needle.

Figure 1 **Schematic drawing of the APFS**



(b) (4)

The intended route of administration is by subcutaneous injection. Injection sites for HCP or caregiver are abdomen, thigh or upper arm. Injection sites for self-administration are abdomen or thigh.

The APFS conditions of use are described in Table 1.

Table 1 APFS Conditions of Use

Biologic product for injection	Tralokinumab, for subcutaneous injection
Dosage capability	APFS dose: 1 mL (150 mg/mL). Total dose per treatment: 2 mL (2 × 150mg/mL → 300 mg in total)
Method of injection	Manual delivery
Packaging configuration	Paperboard box
Environment of use conditions	Non-clinical or clinical environments
Recommended Storage	Store refrigerated at 36°F to 46°F (2-8°C) in the original carton. Do not freeze.
Handling	Acclimate to room temperature 68°F to 77°F ([(b) (4)]25°C) for at least 30 minutes before use. Protect from direct sunlight.

Table 2 APFS Description of Components and Materials of Construction

Component	Function	Material	Supplier
PFS-SA			
Syringe barrel	Primary container for drug product	[(b) (4)] Type I glass	[(b) (4)]
Needle	[(b) (4)]	[(b) (4)]	
Plunger stopper			
Rigid Needle shield [(b) (4)]			
Rigid needle shield [(b) (4)]			
Accessories			
Extended finger flange			
Guard			
Spring			
Body			
Plunger rod			

4.2. Design Requirements

Basic Syringe Description/Requirements

Requirement	Reviewer Comment
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Health Care Proferssionals administering tralokinumab to patients in a clinical use environment. Patients performing self-administration and caregivers performing third party administration to patients. It is intended that patients and caregivers will use th APFS in a non-clinical environment, most commonly at home.
Injection Site	The intended route of administration is by subcutaneous injection. Injection sites for HCP or caregiver are abdomen, thigh

	or upper arm. Injection sites for self-administration are abdomen or thigh.
Injection tissue and depth of injection	Subcutaneous injection
Type of Use (e.g. single use, disposable, reusable, other)	The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function.
Environments of use (e.g. home, clinic)	Clinical Use environment or home use.
Storage conditions and expiry	Store refrigerated at 36°F to 46°F (2-8°C) in the original carton. Do not freeze.
Needle connection (e.g. luer, slip tip, staked)	(b) (4)
Syringe Volume	1 ml
Device materials including lubricant	Syringe Barrel is (b) (4) Type I glass, (b) (4) needle, (b) (4) Plunger stopper needle shield (b) (4), Rigid needle shield (b) (4) (b) (4) See table 2 above and 3.2.P drug-product p. 36/41

Additional Syringe Description/Requirements

Requirement	Reviewer Comment
Hypodermic Needle: length, gauge, and configuration of the tip.	1 mL long glass barrel with a ½ inch 27G (b) (4) needle with RNS
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility criteria (for insulin syringes). Insulin Syringes: The scale on the barrel should be in units of insulin.	The APFS does not contain graduation markings as it is intended to deliver the full labeled volume i.e., the APFS is single use for a fixed dose.
Reuse Durability (for reusable piston syringes): number of times the device can be sterilized and still meet specifications (using sterilization method indicated in the labeling).	N/A
Safety Features (e.g. Needle safety component/device)	The PFS-SA is assembled with a needle safety guard to protect the user from unintended needle stick injuries. The needle safety guard design provides (b) (4) of the safety mechanism to cover the needle following injection.
Automated Functions	N/A
Sterilization method	N/A

*See Design Verification Section for verification of design requirements

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor provided an adequate device deciption for the Pre-Filled Syringe prefilled (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☑

5.1. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☐ Yes ☐ No ☑ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection Needed ☐ N/A
CDRH completed a review of the Quality Systems	☐ Yes ☐ No ☐ N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in Appendix B

5.2. Filing Recommendation

FILING REVIEW CONCLUSION
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☑ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☑ N/A **Site(s) needing inspection:**
Reviewer Comments
Refuse to File Deficiencies: ☐ Yes ☐ No ☑ N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No ☑ N/A

☐ **No Additional Information Requests to add**

6. DEVICE PERFORMANCE REVIEW

6.1. Design Verification/Validation

6.1.1. Device Specification Standards and Guidance Documents

Syringe		**Data Adequate**		
		Yes	**No**	**N/A**
Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☑	☐	☐
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☐	☐	☑
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☑
Needle/Sharps		**Data Adequate**		
		Yes	**No**	**N/A**
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☐	☐	☑
Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☐	☐	☑
Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	☐	☐	☑
Luer Lock		**Data Adequate**		
		Yes	**No**	**N/A**
Connection	ISO 80369-7, Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications **(replaces ISO 594-1 and 594-2 as of 2020) ISO 594-1, Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 1: General requirements ISO 594-2, Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 2: Lock fittings	☐	☐	☑
Other		**Data Adequate**		
		Yes	**No**	**N/A**
[Other]	[Other]	☐	☐	☐

6.1.2. Device Performance Evaluation

3.2.R Device Design Verification

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy/ Delivered Volume	The combination product shall deliver a dose volume (b) (4) mL	Y. Accept of 95%C/97.5%Rtolerance interval, V (b) (4) mL Results: n = 60 min = (b) (4) max = mean StDev	Y. Data provided to support dose volume (b) (4) mL in 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/97.5%Rtolerance interval, V (b) (4) mL. n = 60 min = (b) (4) max = mean StDev
Break loose Force	Maximum break loose force (b) (4)	Y. A constant injection rate/ compression speed (b) (4) mm/min) is applied to each syringe tested. Accept on 95%C/90%R tolerance interval, Requiring a sample size of 60, F (b) (4) Results:n = 60 min = 5N max = 8N mean = 7N StDev = 1N	Y. Data provided to support Maximum break loose force (b) (4) in 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/90%R tolerance interval, F (b) (4) n = 29 min = 6N max = 9N mean = 7N StDev = 1N
Glide Force	Maximum glide force (b) (4)	Y. A constant injection rate/ compression speed (b) (4) mm/min) is applied to each syrin ested. Accept on 95%C/90%R tolerance interval, Requiring a sample size of 60, (b) (4) Results: n = 60 min = 6N	Y. Data provided to support Maximum glide force (b) (4) in 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/90%R tolerance interval, F (b) (4) n = 29 min = 6N max = 8N mean = 7N

		max = 9N mean = 8N StDev = 1N			StDev = 0N
Cap Removal Force	Not applicable	N/A		n/a	n/a
Rigid needle shield pull-off force	The combination product shall have a rigid needle shield pull-off force that is (b) (4)	Y. 95%C/90%R tolerance interval, (b) (4) Results: n = 46 min = 18N max = 24N mean = 21N StDev = 1N	Y. Data provided to support rigid needle shield pull-off force that is (b) (4) in 3 lots	N/A	Y. Accept on 95%C/90%R tolerance interval, (b) (4) n = 46 min = 18N max = 23N mean = 21N StDev = 1N
Needle safety feature activation	(b) (4)	Accept on 0 failures. Reject on 1 or more failures	n = 29 pass = 29 fail = 0	N/A	Accept on 0 failures. Reject on 1 or more failures n = 29 pass = 29 fail = 0
Needle access after injection		(b) (4) Accept on 0 failures. Reject on 1 or more failures	n = 29 pass = 29 fail = 0	N/A	n = 29 pass = 29 fail = 0
Needle safety feature override force after injection		Accept on 95%C/90%R tolerance interval, F (b) (4)	n = 29 min = 141N max = 153N mean = 146N StDev = 3N	N/A	n = 29 min = 116N max = 135N mean = 124N StDev = 4N

Device Free Fall	(b) (4)	No breakage to PFS-SA Accept on 0 failures. Reject on 1 or more failures Deliverable volume V (b) (4) mL Accept on 95%C/97.5%R tolerance interval, V (b) (4) mL (b) (4) Accept on 0 failures. Reject on 1 or more failures	n = 40 pass = 40 fail = 0 min = 1.0mL max = 1.1mL mean = 1.1mL StDev = 0.0mL n = 40 pass = 40 fail = 0	N/A	N/A

Reviewer Comment

The device design verification testing is acceptable. Results include dose accuracy/Delivered volume, Break Loose Force, Glide Force, and Rigid needle shield pull-off force.

3.2.P.2.4.2.4 Performance

"The essential performance requirements of the combination product was evaluated via functionality (break loose and glide force) and deliverable volume tests that were performed as part of specified Drug Product stability studies (M3.2.P.8.1). A summary of the initial (time zero) results are shown in Table 9. The results show that the maximum break loose force, maximum glide force, and deliverable volume were reproducible and consistent between Drug Product lots. The performance of the container closure system was demonstrated to be suitable for injection." P. 16, 3.2.P.2.4 Container Closure System

Table 9 Summary of Container Closure Performance

Stability Lot Number (Stability Protocol Number)	Maximum Break Loose Force (N)	Maximum Glide Force (N)	Deliverable Volume (mL)
83205.145 (DSP-35436)	(b) (4)		
002G13 (DSP-35437)			
ML00029-35 (DSP-354309)			

Analytical procedures for Break Loose Force and Glide Foce is summarized in 3.2.P.5.2 Analytical Procedures

6.1.3. Stability Review Summary

Shelf-life:	shelf life of 36 months for drug product
Storage **conditions**:	storage condition of 5°C
Time period and storage conditions provided for accelerated aging:	25°C ± 2°C/60% ± 5% RH is an accelerated condition
Time period and storage conditions provided for real-time aging:	Storage condition of 5°C with testing scheduled at 0, 3, 6, 9, 12, 18, 24, 36 months and with additional 48 and 60 months for some primary lots. (3.2.P stability summary)

*Endpoint evaluation is provided in section 6.1.2.

Stability studies are monitored at four conditions:

- (b) (4) condition evaluates stability at the temperature at which the Drug Substance is stored (long-term storage condition)
- (b) (4) °C condition evaluates stability at a short term recommended storage condition
- (b) (4) % RH is an accelerated condition
- (b) (4) % RH is a stressed condition

3.2.S.7.1 Stability Summary and Conclusions

The proposed Drug Substance shelf life is (b) (4) months at the long-term storage condition of (b) (4) °C in (b) (4) based on the following:

- (b) (4) months of existing real time data on commitment lots.
- months of real-time data from 2 primary lots (BL2136, 72635-106), (b) (4) months of realtime data from 3 more primary lots (HL2758, HL2777, HN2204), and (b) (4) months of realtime data from 1 more primary lot (KJ0190).

The proposed Drug Substance shelf life is (b) (4) months at the short term storage condition of (b) (4) C in (b) (4) based on the following:

- (b) (4) months of real time data on commitment lots.
- months of real-time data from primary lots (BL2136, 72635-106, HL2758, HL2777, HN2204, and KJ0190).

The proposed Drug Substance shelf life is (b) (4) months in total in (b) (4) This (b) (4) months may be apportioned under a combination of two storage conditions as follows:

- (b) (4) months at the long-term storage condition of (b) (4) °C.
- months at the short-term storage condition of (b) (4) C, noting Drug Substance may (b) (4)

Statistial justification of a sample size of N=60 is provided in 3.2.R.3.4 Design Verification Overview

3.2.P.8.3 Stability Data

From three separate lots:
Real time aging under recommended storage conditions of 5°C is provided for 60 months. This is enough to support the 36 month shelf life. BLF abd GF samples below. Dlivered Volume was also supported up to 60 months with dose volume (b) (4) mL

Table 3 Stability Results for Primary Lot 011G13A (150 mg/mL): Device Functionality Testing

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
Acceptance criteria	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)
5°C ± 3°C							
0	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]
3	(b) (4)						
6							
12							
18							
24							
36							
48							
60							
25°C ± 2°C / 60% ± 5% RH							
0							
1							
3							
6							

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
40°C ± 2°C / 75% ± 5% RH							
0	(b) (4)						
1							
3							

RH = relative humidity;

NP = not performed per the stability protocol

[a] Initial timepoint testing for rigid needle shield removal force and break loose glide force assays were inadvertently not performed. Investigation was conducted and the root cause was inadequate documentation upon shipment of samples for testing.

Table 3 Stability Results for Primary Lot 83205.145: Device Functionality Testing

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
Acceptance criteria	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)
5°C ± 3°C							
0	(b) (4)						
3							
6							
12							
18							
24							
30							
36							
42							
48							
60							
25°C ±2°C / 60% ± 5% RH							
0							
1							
3							
6							

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
40°C ± 2°C / 75% ± 5% RH							
0	(b) (4)						
1							
3							

RH = relative humidity

Reviewer Comments

The sponsor provides stability data for the device with evaluation of shield removal force, Break loose force, and Glide force. The results are acceptable.

The device has (b) (4) needle safety device. The sponsor appears to have evaluated this function per the ISO 23908 standard. Some functions include; Needle safety activation, Needle safety lockout. Both need to be verified after shelf-life, shipping and drop testing. Reliability should be 99%, not 90% per FDA guidance (https://www.fda.gov/media/71142/download)

Needle safety may have been covered through glide force but the reliability should be 99%, not 90% per FDA guidance (https://www.fda.gov/media/71142/download)

An IR is recommended:

1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons:

   The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required.

   Furthermore, the testing should also be performed afrer aging of the device, dropping of the device, and simulated shipping.

   This confidence and reliability information for sharps injury prevention devices can be found in *FDA Guidance: Medical Devices with Sharps Injury Prevention Features* https://www.fda.gov/media/71142/download

An IR was issued December 14, 2020 in CR#3. The response was not adequate. The sponsor provided documentation of the testing of the (b) (4) which was approved through 510(K). This teting is provided, however, the testing does not appear to include any testing with aging of the device (Shelf-Life), dropping of the device, and simulated shipping. It is not clear if the testing is the final manufactured design of the proposed device. Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, combination product manufacturing and preconditioning may impact the performance.

6.1.4. Biocompatibility Evaluation

☑ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]

☐ Biocompatibility was not evaluated **because**: Click or tap here to enter text.

Contact Type and Duration:	Surface-contacting, skin – limited exposure up to 24 h.
Test article:	Syringe Barrel, Needle, Needle adhesive, Plunger stopper, Rigid Needle Shield, (b) (4)
Endpoints Evaluated:	Cytotoxicity, Skin sensitization, Systemic Toxicity (Pyrogenicity), Selection of tests for interactions with blood (not specified)

Extraction Method and Test Methods Acceptability:	Report not provided.

Reviewer Comment

The sponsor claims conformance to Biocompatibility testing (ISO 10993), however, the reports of the testing are not provided. The syringe barrel, , Needle, Needle adhesive, Plunger stopper, are within the fluid patch of the drug and an evaluation of these components is deferred to CDER. However, the Extended finger flange, Needle safety guard, and Plunger rod are not in direct contact with the drug substance and will be evaluated as part of this memo. The sponsor notes Cytotoxicity and Skin sensitization testing, that the testing conforms to the criterion of ISO 10993, however reports are not provided. Classification for the device as a surface device contacting intact skin (Per the 2016 FDA guidance Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" and ISO 10993-1, the Sponsor should evaluate the following endpoints for the plunger: Cytotoxicity, Sensitization, and Irritation. Since the Sponsor has not submitted any report all reports should be submitted. Furthermore,the sponsor does not indicate that skin irritation testing has been performed on the skin contacting components. An information request will be issued to the Sponsor.

Table 16 Primary packaging component materials

Component	Description	Material of Construction	Compliance
Syringe barrel		Type I (b) (4) glass	USP <660>, Ph. Eur 3.2.1, and JP 7.01
Needle	(b) (4)	(b) (4)	ISO 9626
Rigid needle shield (b) (4)			
Rigid needle shield (b) (4)			USP <381> and Ph. Eur. 3.2.9
Adhesive			USP <88>
(b) (4)			(b) (4) Ph. Eur. 3.1.8
Plunger stopper	(b) (4)		USP <381>, USP <87>, USP <88> and Ph.Eur 3.2.9.
(b) (4)			(b) (4) Ph. Eur. 3.1.8

Table 17 Device components

Accessory component	Material of Construction	Compliance
Needle safety guard	(b) (4)	ISO 10993 materials for surface contact <24 hours
Extended finger flange		ISO 10993 materials for surface contact <24 hours
Plunger rod		ISO 10993 materials for surface contact <24 hours

	Date Sent: 10/2/2020	Date/Sequence Received: 10/30/2020
Information Request #1	1. For the extended finger flange, needle safety guard, and plunger rod, which are intact skin contacting, you provide Cytotoxicity and Skin sensitization testing, that you indicate conforms to the criterion of ISO 10993, however you do not provide	

<table>
<tr><td></td><td>reports to verify that conformance. Furthermore, per FDA guidance Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process” the appropriate endpoints based on your contact classification are: Cytotoxicity, Sensitization, and Irritation. Therefore, please provide testing reports for cytotoxicity, sensitization, and irritation for the extended finger flange, needle safety guard and plunger rod.</td></tr>
<tr><td>Sponsor Response</td><td>The device components extended finger flange, needle safety guard and plunger rod have been tested for cytotoxicity, sensitization and irritation according to ISO 10993-5 “Biological Evaluation of Medical Devices Part 5: Tests of In Vitro Cytotoxicity” and ISO 10993-10 “Biological Evaluation of Medical Devices Part 10: Tests for Irritation and Skin Sensitization” Reports containing the results of biocompatibility testing to verify conformance with ISO 10993 are included in module 3.2.R.3.5.3.</td></tr>
<tr><td>Reviewer Comments</td><td>The sponsor provided summary test reports in the response Module 3.2.R.3.5.3 Device Biological Evaluation, Reg-info-dbe and files with Nov. 1, 2020 response. The sponsor tested the finger flange, needle safety guard, and plunger rod for biocompatibility with in vitro Cytotoxity, Skin Irritation, and Skin sensitization according to ISO 10993, part 5 and part 10 as appropriate.

The plunger rod reported in reg-info-cs-01
Studies results summary for TA_12T_50471 [redacted](b) (4) Plunger Rod): qualification of the [redacted](b) (4) plunger rod.

IN VITRO STUDIES, Test Article 12T_50471
<table><tr><th>Test</th><th>Results</th></tr><tr><td>ISO 10993-5
Cell Cytotoxicity Elution Test</td><td>Cytotoxicity: none
Score = 0</td></tr></table>
IN VIVO STUDIES, Test Article 12T_50471
<table><tr><th>Test</th><th>Results</th></tr><tr><td>ISO 10993-10
Intracutaneous Reactivity</td><td>Negligible Irritant
Score = 0.0 (SAL) / Score = 0.1 (SO)</td></tr><tr><td>ISO 10993-10
Guinea Pig Maximization Test</td><td>Nonsensitizer
Score = 0 (SAL, SO)</td></tr></table>
The needle safety guard reported in reg-info-cs-02</td></tr>
</table>

***IN VITRO* STUDIES, Test Article 17-6200-016**

Test	Results
ISO 10993-5 Cell Cytotoxicity Elution Test	Cytotoxicity: none Score = 0

***IN VIVO* STUDIES, Test Article 17-6200-016**

Test	Results
ISO 10993-10 Primary Dermal Irritation	Negligible Irritant PII = 0 (SAL, SO)
ISO 10993-10 Guinea Pig Maximization Test	Nonsensitizer Grade = 0 (SAL, SO)

The finger flange reported in reg-info-cs-03

Studies results summary for TA 13T_58642 (b) (4) finger flange): qualification of the (b) (4) finger flange.

***IN VITRO* STUDIES, Test Article 13T_58642**

Test	Results
ISO 10993-5 Cell Cytotoxicity Elution Test	Cytotoxicity: none Score = 0

***IN VIVO* STUDIES, Test Article 13T_58642**

Test	Results
ISO 10993-10 Intracutaneous Reactivity	Negligible Irritant Score = 0 (SAL,SO)
ISO 10993-10 Guinea Pig Maximization Test	Nonsensitizer Score = 0 (SAL, SO)

The response is adequate.

Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

6.1.5. Sterility Evaluation

☐ Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)

☑ Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

6.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: ☐ **Yes** ☐ **No** ☐ **N/A**	**Mid-Cycle Deficiencies:** ☑ **Yes** ☐ **No** ☐ **N/A**	**Final Deficiencies:** ☐ **Yes** ☐ **No** ☐ **N/A**

Reviewer Comments
The sponsor has not conducted testing after simulated shipping that is representative of the Sponsor's distribution channels.
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No

	Date Sent: 10/2/2020	**Date/Sequence Received:** 10/30/2020
Information Request #2	2. You do not provide testing demonstrating the functionality of your prefilled syringe after simulated shipping. Pleaae provide performance data for your essential performance requirements (i.e., breakloose/glide force and dose accuracy) after simulated shipping representative of your distribution channels.	
Sponsor Response	The tralokinumab drug-device combination product was subjected to simulated shipping per ASTM D4169 and functionality testing of the pre-filled syringe was conducted as part of design verification after simulated shipping. A summary of test results was provided in BLA 3.2.R.3.4 Design Verification, Table 5. This information was sent to the FDA on 06 October 2020 as part of LEO Pharma's responses to the Mid-Cycle Communication Agenda received on 01 October 2020. On 08 October 2020, the FDA confirmed that LEO Pharma's response was adequate to address the FDA request.	
Reviewer Comments	The requested testing was provided in 3.2.R.3.4 Design Verification. The Sponsor provided a new simulated shipping protocol and stated that the new protocol is representative of its distribution channels. Data to demonstrate that the device will perform adequately inclided functionality testing of the pre-filled syringe was conducted as part of design verification after simulated shipping. The simated shipping testing is acceptable.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** 12/14/2020	**Date/Sequence Received:** 12/21/2020
Information Request #3	1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons: The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required. Furthermore, the testing should also be performed after aging of the device, dropping of the device, and simulated shipping. This confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download	
Sponsor Response	(Series 0022)LEO Pharma's response to the information request is included in module 1.11.1. The following new module 3.2.R documents were added to the eCTD: • 3.2.R.3.4.7 Executive Summary safety Claim (b) (4) Needle Guard • 3.2.R.3.4.7 Summary FDA ISO 23908 (b) (4) 510k • 3.2.R.3.4.7 Quality Statement ISO 23908 (b) (4)	

Summary of FDA Guidance/ISO 23908 Bench Testing Filed in (b) (4) needle guards 510(K)s

Device	Submission Type	510(K)	510(K) Clearance Date	Stimulated Clinical Use Testing Filed with FDA (510(k) Reference Section)
(b) (4) needle guard	Traditional 510k	(b) (4)	5/29/2001	As per FDA Draft Supplementary Guidance on the *Content of Premarket Notification {510(k)} Submissions for Medical Devices with Sharps Injury Prevention Features*, March 1995, each of the specified acceptance criteria in the controlled simulated clinical use test were either met or exceeded. Stimulated clinical trials were based on predicative devices (b) (4) series. (b) (4)
(b) (4) {Expansion of Indications for Use}	Traditional 510k		4/28/2006	No additional sharps injury prevention testing required for this premarket notification.
(b) (4) needle guard {New Materials for Plunger Rod}	Special 510k		9/20/2012	As per FDA Guidance *Medical Devices with Sharps Injury Prevention Features*, "If your sharps injury prevention feature is currently legally marketed as a part of another device, you may identify that device in lieu of performing simulated clinical use testing." SSI relies on the clinical use studies completed for the legally marketed devices as well as additional simulated use study for the addition of the various plungers. As per FDA guidance and ISO 23908, 168 devices were tested with zero failures. (b) (4)
(b) (4) (b) (4) needle guard {New Design} (b) (4)	Traditional 510k		3/26/2013	As per FDA Guidance *Medical Devices with Sharps Injury Prevention Features*, 500 devices were tested with zero failures for a *"97.5% confident that the true failure rate was no higher than 0.7% and 99.5% confidence that it is no higher than 1.1%"*. (b) (4)

In 100% of the 512 tested (b) (4) devices the guard completely covered the needle and the lock-out feature was 100% effective; therefore, zero failure was recorded in the present study.
The acceptance criteria from the ISO 239081 and FDA guidance2 on sharps injury prevention feature (i.e. zero device failures out of 500 devices activation) was met.

Reviewer Comments	The sponsor provided documentation of the testing of the (b) (4) which was approved through 510(K). This testing is provided, however, the testing does not appear to include any testing with aging of the device (Shelf-Life), dropping of the device, and simulated shipping. It is not clear if the testing is the final manufactured design of the proposed device.
Response Adequate:	☐ **Yes** ☑ **No, See CR #1**

Follow-On Deficiency	**Date Sent: 1/15/2021**	**Date/Sequence Received: 1/22/2021**
Information Request #3	You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons: The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required. Furthermore, the testing should also be performed after aging of the device, dropping of the device, and simulated shipping. This confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download	

Additional Sponsor Response in Late-Cycle Briefing Package	(Series 0026) *In the Background Package, the Agency cited the 2005 CDRH Guidance for Medical Devices with Sharps Injury Prevention Features as a source of the request to perform testing to a confidence and reliability interval of 95%/99%. This Guidance recommends evaluating 500 devices in a simulated clinical use study to demonstrate sharps injury prevention performance with a 95% confidence interval and 99% reliability. This Guidance does not refer to design verification nor preconditioning and drop testing. Therefore, LEO Pharma does not consider this Guidance applicable to the confidence and reliability parameters for design verification/functional testing of the safety features.* *Furthermore, the Guidance states: "If your sharps injury prevention feature is currently legally marketed as a part of another device, you may identify that device in lieu of performing simulated clinical use testing".* (b) (4) *LEO Pharma has clinical experience with the tralokinumab combination product for the treatment of atopic dermatitis with 3 complaints involving 4 devices with needle safety device deployment failure out of 226,139 devices used, as described in the 21 December 2020 response to an information request (Sequence 0022). This provides additional evidence for the safe use of the needle safety device in a representative clinical environment.* *LEO Pharma agrees that design verification testing of the needle safety performance of the final finished combination product is required. Data to support the needle safety performance and reliability of the combination product has been provided in the BLA (refer to M3.2.R.3.4), and in the 21 December 2020 response. The combination product test articles used for Design Verification testing were produced by the representative manufacturing pro- cess and following preconditioning including real-time aging, drop testing according to ISO 11608-1, and shipping simulation according to ASTM 4169-16. The preconditioning was per- formed individually as is standard practice for design verification testing and described in the recognized international standards for testing of needle-based injection systems. The request for sequential preconditioning by the Agency is beyond the requirements of any regulatory guidance or medical device standard known to LEO Pharma.* *Selection of confidence intervals and reliability values for design verification of the tralokinumab combination product was done in accordance with risk-based sampling criteria which consider the potential impact to the user if the feature does not perform as intended. This ap- proach has traditionally been accepted by the Agency for a range of combination products in clinical trials and in marketing applications and resulted in the sample sizes shown in the LEO Pharma communication of 21 December 2020. The sample sizes were also included in the original BLA (refer to M3.2.R.3.4).* *In conclusion, the safety and reliability of the* (b) (4) *has been demonstrated based on the design verification performed for the tralokinumab combination product, extensive use of* (b) (4) *for other legally mar- keted products and further supported by the complaint data from the Tralokinumab clinical study. LEO Pharma respectfully requests that the Agency reconsider its position on this sub- stantive review issue.*

Reviewer Comments	The sponsor provided documentation of the testing of the (b) (4) (b) (4) which was approved through 510(K) (As referenced for sequence 0022). This was provided in response to IR#3. This testing is provided, however, the testing did not include any testing with aging of the device (Shelf-Life), dropping of the device, and simulated shipping. The sponsor references section 10 of the guidance, p. 10, under Simulated Clinical Use Testing, where it says "For devices that include sharps injury prevention features, we recommend that you conduct simulated clinical use testing and provide an analysis of the results from simulated clinical use testing and a summary of the results and conclusions. *If your sharps injury prevention feature is currently legally marketed as a part of another device, you may identify that device in lieu of performing simulated clinical use testing.*" However, the referenced guidance is specifically for 510(k) submissions. Eventhough the argument is for 510k cleared devices, they cannot leverage this data because of differences in design/mfg/handling of those products compared to theirs. They didn't provide a comparison of performance. In their response, "LEO Pharma agrees that design verification testing of the needle safety performance of the final finished combination product is required" They had provided the sample size. The additional preconditioning we are requesting is representative of intended use. Their sampling is unacceptable as we explained. The agency determine a reliability of 99% is appropriate for needle safety in general because of the severity of the risk with needle stick (HIGH). A reliability of 90% and 97.5% is not acceptable and would deviate from how we evaluate other submissions.
Response Adequate:	☐ **Yes** ☑ **No, See CR 1# Sent on** Click or tap to enter a date.

7. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	The combination product shall deliver a dose volume (b) (4) mL	Y
Break loose Force	Maximum break loose force (b) (4)	Y
Glide Force	Maximum glide force (b) (4)	Y

Cap Removal Force	N/A	N/A
Rigid need;e shield pull-off force	The combination product shall have a rigid needle shield pull-off force that is (b) (4)	Y

Reviewer Comments

The Sponsor has included the EPRs of the device constituent parts of the combination product in the release testing of the device. This is an acceptable control strategy. The needle safety activation was notadequately evaluated. An IR was sent on December 14, 2020, however, the sponsor presented a resppnse based on prior approval of the device through the 510(k) process, however, testing for shelf-life and shipping is needed with the current PFS product. A major deficiency is recommended.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

7.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

The sponsor provided an adequate device desciption for the Pre-Filled Syringe prefilled (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function. The sponsor had conducted performance testing of the device demonstrating that the device met Essential Performance Requirements for validation, after simulated shipping, and aging(shelf-life). While the sponsor provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. The testing is not adequate mostly for sample size and reliability of the needle safety feature which is essential for preventing accidental needle sticks.

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Filing/74-Day Information Requests

8.2. Mid-Cycle Information Requests

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

1. For the extended finger flange, needle safety guard, and plunger rod, which are intact skin contacting, you provide Cytotoxicity and Skin sensitization testing, that you indicate conforms to the criterion of ISO 10993, however you do not provide reports to verify that conformance. Furthermore, per FDA guidance *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"* the appropriate endpoints based on your contact classification are: Cytotoxicity, Sensitization, and Irritation. Therefore, please provide testing reports for cytotoxicity, sensitization, and irritation for the extended finger flange, needle safety guard and plunger rod.
2. You do not provide testing demonstrating the functionality of your prefilled syringe after simulated shipping. Pleaae provide performance data for your essential performance requirements (i.e., breakloose/glide force and dose accuracy) after simulated shipping representative of your distribution channels.

8.3. Interactive Information Requests

8.3.1. Interactive Information Requests sent on 12/14/2020

1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons:

   The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required.

   Furthermore, the testing should also be performed after aging of the device, dropping of the device, and simulated shipping.

   This confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 21, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761180
Product Name, Dosage Form, and Strength:	(b) (4) (tralokinumab-ldrm)[a] Injection 150 mg/mL
Product Type:	Combination Product (Biologic-Device)
Device Constituent:	Pre-filled Syringe
Rx or OTC:	Prescription (Rx)
Applicant Name:	Leo Pharmaceuticals
FDA Received Date:	April 27, 2020
OSE RCM #:	2020-883 and 2020-885
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting):	Jason Flint, MBA, PMP
DMEPA Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

[a] FDA found the proposed suffix -ldrm conditionally acceptable during the review of suffixes submitted to BLA 761180.

1 REASON FOR REVIEW

We reviewed the human factors (HF) validation study report and proposed labels and labeling submitted under BLA 761180 for tralokinumab-ldrm injection. This is a combination product with a proposed pre-filled syringe (PFS) device constituent part that is intended for the treatment of moderate-to-severe atopic dermatitis in adult patients.

1.1 PRODUCT DESCRIPTION

The (b) (4) pre-filled syringe is a single entity, fixed dose, disposable biologic-device combination product. The single-dose pre-filled syringe constituent enables subcutaneous injection of 150 mcg/mL of the biologic, with a complete initial dose of 600 mg constituting four injections, followed by a maintenance dose of 300 mg constituting two injections.

(b) (4) is available in package sizes containing a carton of 2 syringes or a multi-pack carton containing 2 cartons each with 2 syringes (total of 4 syringes of multi-pack carton).

1.2 REGULATORY HISTORY

On March 1, 2019, the Applicant submitted a use-related risk analysis (URRA) and HF validation study protocol. Our review recommended that the Applicant address the identified areas of concern prior to commencing the HF validation study.[b]

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Request	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[b] Schlick, J. Human Factors Validation Study Protocol Review for Tralokinumab (IND 123797). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 23. RCM No.: 2019-484.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide a summary of the use-related risk analysis (URRA), HF study design, errors/close calls/use difficulties observed with critical and non-critical tasks (Table 3 and Section 4.3 respectively), and our analysis to determine if the HF study results support the safe and effective use of the proposed product. We also address the labels and labeling in Section 3.5.

3.1 SUMMARY OF STUDY DESIGN

STUDY METHODOLOGY

We reviewed the HF validation study methodology and found that the Applicant did not incorporate some of our recommendations from our previous HF validation study protocol review. They include the following:

1. No use scenario or knowledge task to test users' understanding that the initial dose requires four syringes to administer the complete dose.

   We sought input from the clinical review team to assess the clinical impact of an underdose with the initial 600 mg dose that requires 4 x 150 mg PFS. The clinical review team indicated that a single initial underdose would not be clinically meaningful given the therapeutic and adverse event profile of the product. Thus, given the product characteristics, we determined the lack of assessing whether users (HCP, caregiver, or patient) understand that four injections are required to give a full initial dose of 600 mg does not require revisions to the study methodology and additional HF validation study data.

2. No healthcare professional (HCP) user group.

   We reviewed the URRA for the proposed product and agree that the tasks evaluated are comprehensive and appropriate for the proposed product. We also reviewed the URRA to ensure that all potential use errors and risks involved in using the proposed product, including known use issues with currently marketed products, have been considered and adequately mitigated. In addition, we did not identify any new, differing, or unique risks for the proposed product as compared to other approved pre-filled syringes intended for use by healthcare professionals. Thus, we determined the lack of the HCP user group in the HF validation study does not require revisions to the study methodology and additional HF validation study data.

In addition, we note the HF validation study included an adolescent patient user group; however, the proposed indication is for adult patients. Thus, we focused our review of the results on the adult patient and caregiver user groups.

Table 2 provides a summary of the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	<table><tr><th>User Group</th><th>Trained</th><th></th></tr><tr><td>Adult AD Patients</td><td>N=7</td><td>N=15</td></tr><tr><td>Adolescent AD Patients</td><td>N=7</td><td>N=15</td></tr><tr><td>AD Caregivers</td><td>N=7</td><td>N=15</td></tr><tr><td>Subtotal</td><td>N=21</td><td>N=45</td></tr></table>
Training	In the untrained arm, no training was provided to participants. The product and IFU were made available to participants to use as they normally would.
Test Environment	Simulated a typical domestic use environment
Simulated Use Session Structure	Scenario #1 – Inject 300 mg dose (2 injections); Scenario #2 – Inject another 300 mg dose (2 injections). Root Cause Analysis Knowledge Assessment

3.2 RESULTS AND ANALYSES

Table 3 describes the errors/close calls/use difficulties observed with critical and essential tasks in the HF study, the Applicant's analyses and proposed mitigation strategies, and DMEPA's analyses and recommendations.

TABLE 3: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS

Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Open the Carton	2 Use Difficulties 1 untrained adult and 1 untrained caregiver	Participants ripped the carton open from the side.	All participants stated they normally open cartons from the side, and they assumed the study carton to be the same. All noticed 'Open here' graphic on front panel and self-corrected for 2nd simulated dose.	No additional mitigation is necessary. No use errors were committed.	Based on the Applicant's use-related risk analysis (URRA), the user could damage the device or open a tampered carton without noticing the tampering at the 'Open here', and this could lead to injection of unsterile product. Our review of the study results did not identify subjective feedback indicating confusion with the carton labeling. Our review of the carton labeling finds that 'Open here' is located on the front flap to alert users where to open. Additionally, all participants

					noticed the 'Open here' graphic on the front panel for the second simulated dose and self-corrected. We reviewed the Applicant's root cause analysis and agree with their assessment. Thus, we find the residual risk acceptable for these errors, and we have no recommendations at this time.
Remove device from the carton without activating the needle guard	1 Use Difficulty Untrained Caregiver	Participant squeezed needle guard clips when inspecting the syringe.	He assumed he had to release the clips to unlock the device. He soon realized that all he needed to do was remove the needle cover and his confusion was alleviated.	No additional mitigation is necessary. No use errors were committed.	Based on the Applicant's URRA, the patient would receive a partial dose or have the dose delayed (patient inconvenience) as they sought a replacement syringe. Our review of the study results did not identify subjective feedback indicating confusion with the IFU, and we reviewed the IFU section that instructs users how to remove the device. We did not identify any additional risk mitigations to further reduce the occurrence of this use difficulty. We also reviewed the Applicant's root cause analysis and agree with their assessment. Thus, we find the

					residual risk acceptable for this use difficulty, and we have no recommendations at this time.
Do not use contaminated needle	1 Use Error 1 Untrained Adult Patient	Use Error - Used contaminated needle/device	(b) (6): Untrained adult patient (3rd use) was nervous handling the first exposed needle and dropped it. She stated that if it had been a real situation she would have disposed of the syringe, which represents a study artefact.	No additional mitigation is necessary. Although use errors on a safety-critical task were committed, the occurrence of a contaminated needle would be improbable (< 1/1,000,000). 2 out of 3 use errors for using contaminated needle were considered study artefact since participants wouldn't have acted that way in the real world.	Based on the Applicant's URRA, the harm to a patient using a contaminated needle could result in infection. The participant's subjective feedback indicated she was nervous and would have disposed of the syringe in real life. We note the Applicant's assessment that the probability of occurrence is improbable because the error occurred in a study of 30 participants; however, we generally focus on the harm of an error. Additionally, we disagree with the assessment that consistent training will be done by HCPs to assess suitability to self-inject prior to home use. We note the IFU does not instruct the user what to do if the needle touches an unsterile surface and is contaminated. Thus, we provide a recommendation in Section 4.2

				Lay- users are intended to be trained and assessed to be suitable for self-injection by HCPs prior to home use.	to address this use error.
Activate and deploy needle guard	2 Use Errors 2 Untrained Caregivers	Failed to activate and deploy needle guard	(b) (6) (3rd use) & (b) (6) (1st, 2nd, and 3rd use): Untrained caregivers. Both believed that they did the same thing as with their successful injections, namely pushing until the plunger stopped and applying the same force at the end of injection. It is concluded that they both stopped pushing when they felt a certain resistance level, whether that be from the stopper reaching the end of travel or the resistance from the needle guard activation clips. Both were successful on their final (4th) injection, which suggests there may have been a learning effect.	No additional mitigation is necessary. Although use errors on a safety-critical task were committed, the occurrence of a needlestick injury due a cascade of use errors of not deploying the needle guard and incorrectly disposing the used device disposal would be improbable (<	Based on the Applicant's URRA, the harm of not activating the needle guard could lead to the transmission of blood borne pathogens resulting in a serious infection. Our review of the study results did not identify subjective feedback indicating confusion with the IFU. We reviewed the IFU section In Steps 3c and 3d that instructs users to "… All the medicine is injected when you cannot push the plunger head any further. Lift your thumb off the plunger head. The needle will automatically move back inside the syringe body and lock into place" and includes corresponding graphics.
	2 Use Difficulties 1 Untrained Adult Patient and 1 untrained	Difficulty deploying the needle guard	(b) (6): Untrained adult patient (2nd and 4th use) was confused by the inconsistency of the device clicking when the needle guard was activated. She stated she was concerned about not hearing the click		

	Caregiver		and would have called her HCP. She read the IFU more thoroughly and noticed that there was no indication that the device should click. (b) (6): Untrained caregiver (3rd use) kept her thumb on the plunger head as she removed the needle from injection site and was confused about the needle guard not activating immediately. After consulting the IFU, she understood what happened. She said she was "probably confident" that she had delivered a full dose. In the real world, she would have called her HCP to follow-up.	1/1,000,000). Participants understood their error after thoroughly reviewing the IFU or understood to contact their HCP to discuss. Lay-users are intended to be trained and assessed to be suitable for self-injection by HCPs prior to home use.	Additionally, the participants completed this step in subsequent injections as they became more familiar with the task. Thus, we find the residual risk acceptable and have no recommendations at this time.
Give 2nd syringe to complete full dose (2 syringes required to achieve 300 mg dose	3 Use Errors 2 Untrained Adult Patients 1 untrained Caregiver	Failed to deliver second syringe	(b) (6): Untrained adult patient (1st and 2nd dose) is a Dupixent user and only glanced at the IFU. He assumed the 2nd syringe was a "booster shot". He didn't notice the repeat symbol on the carton label or in the IFU. He also commented that in the real world he would have been shown by his doctor how to inject, suggesting that the untrained scenario was not realistic for this participant.	No additional mitigation is necessary. Although use errors on a safety-critical task were committed, a missed/ incomplete dose would	Based on the Applicant's URRA, the harm to a patient of not injecting the second syringe to complete a full dose results in an incomplete dose and effects efficacy if the error occurs multiple times. Our review of the study results and subjective feedback identified negative transfer from

			[redacted]: Untrained adult patient (1st and 2nd use) opened the carton at the ends and then ripped the "repeat" symbol on the carton. During discussion she said the if she had opened the box properly and read the instructions properly then she would have known to repeat. [redacted]: Untrained caregiver (1st and 2nd dose) didn't read the IFU for either the 1st or 2nd dose, but noticed the "repeat" symbol on the carton label after the 2nd dose and stated, "I should have read the instructions the first time". During discussion, it became clear that when administering the first dose she had assumed that the second syringe was for the next dose. She understood that she made an error and should have injected both syringes and said she would have checked with her doctor about the underdose.	not have resulted in serious harm to the patient. All participants understood their error after thoroughly reviewing the IFU. Lay-users are intended to be trained and assessed to be suitable for self-injection by HCPs prior to home use.	another product where injecting one syringe completes the full dose as a contributing factor to the use error, which can be difficult to overcome. Additionally, errors were attributed to not reading the IFU and looking only at the pictures in the IFU, not seeing the repeat symbol on the carton before the first injection, and ripping the carton where the repeat symbol is located on the underside of the principal display panel. We contacted the clinical review team to assess the clinical consequences of multiple underdoses. The clinical review team noted that the 300 mg dose (2 syringes) was more efficacious than a 150 mg dose (one syringe), and that the treatment-related adverse events were similar between the two doses. However, the review team stated that the comparative risk versus benefit between the two doses was not clinically meaningful. Our review of the of the carton labeling and IFU did not identify
	1 Close Call Untrained Adult Patient	Delayed injection of 2nd syringe	[redacted]: Untrained adult patient (1st dose) didn't read the IFU, because he unknowingly dropped it when he opened the first carton. After looking at the carton and noticing the carton label to repeat injection, he realized his error and self-corrected. He repeatedly stated that in the real	No additional mitigation is necessary. No use errors were committed.	

			world, he would have been shown how to use the device first by his HCP and he wouldn't have done what he did during the study without checking with his doctor. This close call is likely to represent a study artefact, since he would not be given the device without prior training.		additional labeling revisions to further mitigate this risk. Thus, we find the residual risk acceptable and have no recommendations at this time.
Dispose of device in sharps container	1 Use Error 1 Untrained Adult	Failed to discard syringes in sharps container	(b) (6): Untrained adult patient (all uses) didn't read the IFU because he unknowingly dropped it when he opened the first carton. He was able to deploy the needle guard for all uses, which provided the first level of needle safety. He explained that he re-uses and changes the needles in his current injection device. He repeatedly stated that in the real world, he would have been shown how to use the device first by his HCP and he wouldn't have done what he did during the study without checking with his doctor. This use error is likely to represent a study artefact, since he would not be given the device without prior training.	No additional mitigation is necessary. Although use errors on a safety-critical task were committed, the occurrence of a needlestick injury due a cascade of use errors of not deploying the needle guard and incorrectly disposing the used device disposal would be improbable (< 1/1,000,000).	Based on the Applicant's URRA, the harm of not disposing the device in a sharps container could lead to the transmission of blood borne pathogens resulting in a serious infection. Our review of the study results did not identify subjective feedback indicating confusion with the instructions for use, and we reviewed the IFU section that instructs users to dispose of the PFSs in a sharps container. We did not identify any additional risk mitigations to further reduce the occurrence of this use difficulty. Based on our overall assessment of the study results and labels and labeling, we find the residual risk is acceptable and have no recommendations at this time.

				Participants understood their error after thoroughly reviewing the IFU or understood to contact their HCP to discuss. Lay-users are intended to be trained and assessed to be suitable for self-injection by HCPs prior to home use.	

3.3 ANALYSIS OF NON-CRITICAL TASKS

We acknowledge that there were use-related issues (e.g. use errors, close calls, or use difficulties) with non-critical tasks. The Applicant categorized "choose and prepare injection site" to be non-critical; however, we consider this task to be critical[c] because based on the Applicant's URRA, choosing an incorrect injection site may result in intradermal injection or injection into a blood vessel. We note the Applicant provided the number of participants who completed this task correctly but did not provide any root cause analysis or subjective feedback information in the report. Thus, we sent an Information Request (IR) to the Applicant to obtain the root cause analysis and subjective feedback for this task (see Appendix F). The

[c] Draft Guidance for Industry: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development. 2016. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Applying Human Factors and Usability Engineering to Medical Devices. https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Applicant's IR response on August 19, 2020 indicated that one untrained adult chose the arm stating, "that was a logical place to inject", and one untrained caregiver chose the buttocks "since he saw healthcare professionals inject into the buttocks."

The Applicant noted in their URRA that wrong injection site selection could lead to injection into blood vessel but would not require professional medical intervention, and an intradermal injection would result in injection pain. We sought input from the clinical review team to determine if they agree with this assessment. The medical officer responded via email on August 26, 2020 that the data submitted in the BLA was inconclusive, but it appears unlikely that an inadvertent single intravascular injection would cause a higher risk of an allergic reaction than a SC injection. We note that all participants who committed a use error self-corrected for the next three simulated injections. Based on our overall assessment of the study results and labels and labeling, and input from the clinical review team, we find the residual risk acceptable and have no recommendations at this time.

Additionally, our review noted a change in the categorization of the task "Allow product to come to room temperature" in the URRA. The URRA submitted with the HF validation study protocol for our review on March 1, 2019 categorized this task as critical. The URRA submitted with the HF validation study results on April 27, 2020 categorized the task as non-critical. The URRA notes that if the medication is warmed using an external heat source, serious injury could occur due to immunogenic, allergic, or anaphylactic reactions. Thus, we consider this task to be a critical task.[d] The HF validation study results include the results on the knowledge task question for this task and we note that all participants answered the knowledge task question correctly.

3.4 LABELS AND LABELING

We identified concerns with the label and labeling from a medication error perspective. See the table in Section 4.1 for the Division and the table in Section 4.2 for the Applicant that include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation. At this time, we have determined that these recommendations do not require additional human factors validation study data to be submitted for review.

[d]Draft Guidance for Industry: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development. 2016. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Applying Human Factors and Usability Engineering to Medical Devices. https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4 CONCLUSION

The results of the HF validation study identified failures, close calls, and use difficulties with critical tasks. Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. In Section 4.1 (Division) and Section 4.2 (Applicant), we have provided recommendations and we recommend that the revisions be implemented prior to approval of the BLA. In this particular instance, we have determined that that these changes can be implemented without additional HF validation testing to be submitted for review.

4.1 RECOMMENDATIONS FOR THE DIVISION

Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	Identified Issue	Rationale for Concern	Recommendation
Highlights of Prescribing Information			
1.	No Comments		
Full Prescribing Information			
1.	The carton contains the following statement "Do not freeze", but this statement is not found in the proposed Prescribing Information	This important storage information could be overlooked leading to a medication error.	Include the following statement in Section 16.2 "Storage and Handling": "Do not freeze. Do not use (b) (4) if it has been frozen."

4.2 RECOMMENDATIONS FOR LEO PHARMACEUTICALS

Identified Issues and Recommendations for Leo Pharmaceuticals (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Product Design			
1.	The human factors validation study identified use errors with the critical task of giving a second syringe to complete the full 300 mg dose.	Based on your use-related risk analysis (URRA), the harm to a patient of not injecting the second syringe to complete a full dose results in an incomplete dose and affects efficacy if the error occurs multiple times.	Consider packaging the 2 syringes together within the carton (for example in a sleeve) to minimize the risk of users only administering one syringe. Additionally, consider including a statement on the sleeve, "Administer both syringes to get your full prescribed dose" using bold font, color, or some other means to ensure the statement is prominent.
Instructions for Use (IFU)			
1.	The statement in Step 4 of the IFU does not include an introductory statement to delineate what to do if the dose is 600 mg or 300 mg. Additionally, the heading for Step 4 does not describe the 4 syringes	This lack of clarity could cause confusion with use of the product, resulting in an underdose.	Revise the heading of Step 4 (b) (4) to, "Injecting the next syringe." Additionally, revise the statement, (b) (4) (b) (4) to read, • "To get your full prescribed initial dose of 600 mg, you will need to give 4 injections." • "To get your full prescribed dose of 300 mg, you will need to give 2 injections." Additionally, revise the Note statement (b) (4) (b) (4)

	needed to complete the 600 mg initial dose.		to read, "Make sure you give your next injection within the same body area, but at least 1 inch (3 cm) away from where you injected (b) (4) in Step 3."
2.	The human factors validation study identified use errors with the critical task "Do not use contaminated needle." We note Step 3a of the IFU includes the statement, "Do not touch the needle, or let it touch any surface." However, the IFU does not include instructions for the user to follow if the needle is contaminated.	Use of a contaminated needle may result in infection.	Add information to Step 3a of the IFU following the statement, "Do not touch the needle, or let it touch any surface" to provide users with instructions if a needle becomes contaminated.
Container Labels			
1.	The expiration date format is not defined on the proposed label.	Certain expiration date formats can lead to medication errors.	As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to

			represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Carton Labeling			
1.	The strength statement is unclear as to whether each syringe contains 150 mg or the complete contents of the carton contains 150 mg.	The dose requires multiple syringes to complete a dose. A lack of clarity as to the amount in each syringe could lead to the incorrect number of syringes injected to complete a dose.	Revise the strength statement on the principal display panel and side panels to read: "150 mg/mL per syringe"
2.	Your proposed packaging configurations (b) (4)	Given your proposed packaging configurations (b) (4) (b) (4) (b) (4) could lead to unintended confusion (b) (4) (b) (4)	Remove the statements (b) (4) (b) (4)

	(b) (4)		
3.	The expiration date format is not defined on the proposed label.	Certain expiration date formats can lead to medication errors.	As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for [redacted] received on April 27, 2020 from Leo Pharmaceuticals.

<table>
<tr><th colspan="2">Table 5. Relevant Product Information for [redacted]</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>tralokinumab-ldrm</td></tr>
<tr><td>Indication</td><td>The treatment of moderate-to-severe atopic dermatitis in adult patients.</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>Injection</td></tr>
<tr><td>Strength</td><td>150 mg/mL</td></tr>
<tr><td>Dose and Frequency</td><td>An initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week. [redacted] a dosage of 300 mg every 4 weeks may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment.</td></tr>
<tr><td>How Supplied/Container Closure</td><td>supplied in single-dose prefilled syringes with needle guard. Each prefilled syringe with needle guard.
Available in pack sizes containing 2 or 4 pre-filled syringes with needle guard.
<table>
<tr><th>Pack Size</th><th>NDC #</th></tr>
<tr><td>Multipack - 2 cartons (4 syringes)</td><td>NDC 50222-346-04</td></tr>
<tr><td>Carton of 2 syringes</td><td>NDC 50222-346-02</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Store refrigerated at 36°F to 46°F (2°C to 8°C)</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 31, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, tralokinumab and IND 123797. Our search identified one previous review[e], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design and Results

The HF study results review can be accessible in EDR via:

\\CDSESUB1\evsprod\bla761180\0001\m3\32-body-data\32r-reg-info\reg-info-hfe-report.pdf

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. INFORMATION REQUEST

For the task, Choose and Prepare the Injection Site, we note the Applicant only provided the number of users who completed this task correctly (i.e., 62/66), and did not provide any root cause or subjective feedback information in the report. We sent an Information Request to the Applicant to obtain the root cause analysis and subjective feedback for this task. The Applicant responded on August 19, 2020 with this information.

The Information Request response can be accessible in EDR via:

\\CDSESUB1\evsprod\BLA761180\0009\m1\us\clinical.pdf

[e] Schlick, J. Human Factors Validation Study Protocol Review for Tralokinumab (IND 123797). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 23. RCM No.: 2019-484.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Leo Pharmaceuticals.

- Container label received on April 27, 2020 - \\CDSESUB1\evsprod\bla761180\0001\m1\us\draft-carton-container-labels-syr.pdf
- Container label sample received on April 27, 2020 - \\CDSESUB1\evsprod\bla761180\0001\m1\us\draft-carton-container-labels-syr-sample.pdf
- Carton labeling received on April 27, 2020 - \\CDSESUB1\evsprod\bla761180\0001\m1\us\draft-carton-container-labels-carton.pdf \\CDSESUB1\evsprod\bla761180\0001\m1\us\draft-carton-container-labels-carton-tert.pdf
- Carton labeling inner flap received on April 27, 2020 - \\CDSESUB1\evsprod\bla761180\0001\m1\us\draft-carton-container-labels-carton-inner.pdf
- Carton labeling sample received on April 27, 2020 - \\CDSESUB1\evsprod\bla761180\0001\m1\us\draft-carton-container-labels-carton-sample.pdf
- Instructions for Use received on April, 27, 2020
- Prescribing Information (Image not shown) received on April 27, 2020 - \\CDSESUB1\evsprod\bla761180\0001\m1\us\annotated-draft-labeling-text.pdf

5 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MADHURI R PATEL
01/21/2021 03:09:53 PM

MILLIE B SHAH
01/21/2021 04:12:33 PM

JASON A FLINT
01/21/2021 04:16:31 PM

MISHALE P MISTRY
01/21/2021 04:41:51 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 21, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761180
Product Name and Strength:	(b) (4) (tralokinumab-ldrm) injection, 150 mg/mL
Applicant/Sponsor Name:	Leo Pharmaceuticals
OSE RCM #:	2020-883-1 and 2020-885-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 12, 2020 for (b) (4). Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for (b) (4) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective. We note the Applicant revised the strength statement (b) (4); however, we continue to recommend the strength statement on the principal display panel (PDP) and side panels to read "150 mg/mL per syringe" to clarify 150 mg/mL is the strength for each syringe.

3 RECOMMENDATIONS FOR LEO PHARMACEUTICALS

We recommend the following be implemented prior to approval of this BLA:

A. For the container labels, revise the strength to read "150 mg/mL" (b) (4) (b) (4).

[a] Schlick J, Patel M. Label and Labeling Review for (b) (4) (BLA 761180). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 21. RCM No.: 2020-883 and 2020-885.

B. On the carton labeling, we continue to recommend revising the strength statement on the principal display panel and side panels to read: “150 mg/mL per syringe” for clarity.

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/s/

MADHURI R PATEL
01/21/2021 03:32:51 PM

MILLIE B SHAH
01/21/2021 04:14:33 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	12/23/2020		
To:	Strother Dixon		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	Other
From	Stephen M. Retta OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C GHDB		
Subject	BLA 761180, (b) (4) (Tralokinumab) ICC2000441		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 12/23/2020 ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☑ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761180
Sponsor	Leo Pharma Inc.
Drug/Biologic	(b) (4) (b) (4) (Tralokinumab)
Indications for Use	is proposed for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately contolled with topical prescription therapies or when those therapies are not advisable.
Device Constituent	Pre-Filled Syringe
Related Files	BLA 761180

Important Dates	
Filing	June 11, 2020
74-Day Letter	June 22, 2020
Midcycle Meeting/IRs due	September 25, 2020
Final Lead Device Review Memo Due	December 18, 2020
PDUFA Date	November 13, 2020

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☑ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☑ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

1. You provided a response to an information request dated, December 14, 2020, which provided documentation of (b) (4) (b) (4) associated 510(k) references to address our request for data verifying the needle safety performance of your combination product at an appropriate reliability limit

(95% confidence /99% reliability) and pre-conditioning (aging, drop testing and shipping). While the testing provided evidence for performance of the 510(k) cleared needle safety device component, the testing did not include testing of your final finished combination product or testing after the requested representative preconditioning (aging of the device, dropping of the device, and simulated shipping). Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, combination product manufacturing and preconditioning may impact the performance. Failure of the needle safety device to perform adequately may result in accidental needle sticks. Provide testing demonstrating that your final finished combination product needle safety performance (needle safety activation and lockout) can meet a confidence and reliability of 95%/99% after aging of the device to the proposed shelf-life, drop testing and simulated shipping per ASTM 4169-16 *Standard Practice for Performance Testing of Shipping Containers and System*s sequentially.

The recommended confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

3. PURPOSE/BACKGROUND

3.1. Scope

Leo Pharma Inc. is requesting approval of a prefilled syringe (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The device constituent of the combination product is a Pre-Filled Syringe.

Choose an item. has requested the following consult for review of the device constituent of the combination product:

Please review the device component of this original BLA submission.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

☒ Device performance
☒ Biocompatibility of the patient contacting components
☐ Sterility
☒ Stability – device performance on stability
☒ Essential Performance Requirements (EPR) Control strategy
☐ Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
(b) (4) (Tralokinumab)	The APFS is intended to deliver a 1 mL injection of tralokinumab via subcutaneous delivery to patients with moderate to severe atopic dermatitis (AD).
Pre-Filled Syringe	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	3.2.R
0001	3.2.P
0022	3.2.R.3.4.7

4. DEVICE DESCRIPTION

4.1. Device Description

From 3.2.R.3 reg-info-device-discription. The combination product consists of an **accessorized prefilled syringe** (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab.

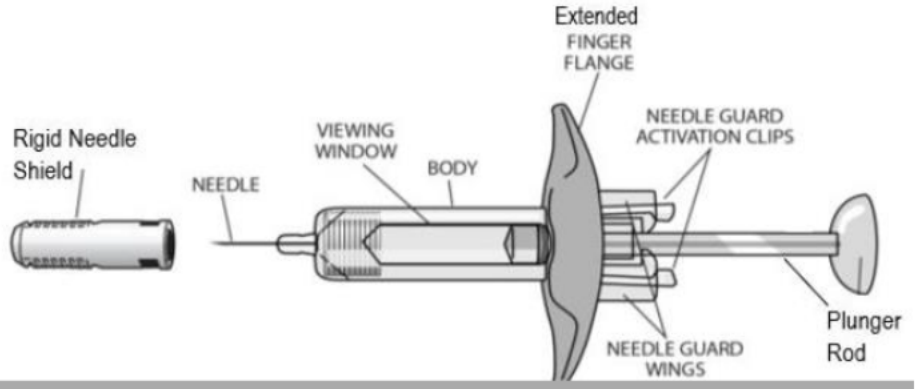
One intended user population includes HCPs administering tralokinumab to patients in a clinical use environment. A second intended user population includes patients performing self-administration and caregivers performing third party administration to patients. It is intended that patients and caregivers will use th APFS in a non-clinical environment, most commonly at home.

The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function. It is designed to administer a 1 mL fixed dose of 150 mg/mL tralokinumab, 2 × 1 mL APFS provides one full 300 mg dose. The APFS is supplied pre-assembled and ready for use.

The APFS consists of a prefilled syringe sub-assembly (PFS-SA) consisting of a 1 mL long syringe barrel with a ½ inch 27 gauge (b) (4) needle, rigid needle shield(RNS) and plunger stopper. The accessorized part consists of a needle safety guard, plunger rod and extended finger flange. The needle safety guard is composed of a needle guard body with activation clips and wings.

The prefilled syringe is (b) (4) in needle.

Figure 1 **Schematic drawing of the APFS**



(b) (4)

The intended route of administration is by subcutaneous injection. Injection sites for HCP or caregiver are abdomen, thigh or upper arm. Injection sites for self-administration are abdomen or thigh.

The APFS conditions of use are described in Table 1.

Table 1 APFS Conditions of Use

Biologic product for injection	Tralokinumab, for subcutaneous injection
Dosage capability	APFS dose: 1 mL (150 mg/mL). Total dose per treatment: 2 mL (2 × 150mg/mL → 300 mg in total)
Method of injection	Manual delivery
Packaging configuration	Paperboard box
Environment of use conditions	Non-clinical or clinical environments
Recommended Storage	Store refrigerated at 36°F to 46°F (2-8°C) in the original carton. Do not freeze.
Handling	Acclimate to room temperature 68°F to 77°F ((b) (4) 25°C) for at least 30 minutes before use. Protect from direct sunlight.

Table 2 APFS Description of Components and Materials of Construction

Component	Function	Material	Supplier
PFS-SA			
Syringe barrel	Primary container for drug product	(b) (4) Type I glass	(b) (4)
Needle	(b) (4)	(b) (4)	
Plunger stopper			
Rigid Needle shield (b) (4)			
Rigid needle shield (b) (4)			
Accessories			
Extended finger flange			
Guard			
Spring			
Body			
Plunger rod			

4.2. Design Requirements

Basic Syringe Description/Requirements

Requirement	Reviewer Comment
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Health Care Proferssionals administering tralokinumab to patients in a clinical use environment. Patients performing self-administration and caregivers performing third party administration to patients. It is intended that patients and caregivers will use th APFS in a non-clinical environment, most commonly at home.
Injection Site	The intended route of administration is by subcutaneous injection. Injection sites for HCP or caregiver are abdomen, thigh

	or upper arm. Injection sites for self-administration are abdomen or thigh.
Injection tissue and depth of injection	Subcutaneous injection
Type of Use (e.g. single use, disposable, reusable, other)	The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function.
Environments of use (e.g. home, clinic)	Clinical Use environment or home use.
Storage conditions and expiry	Store refrigerated at 36°F to 46°F (2-8°C) in the original carton. Do not freeze.
Needle connection (e.g. luer, slip tip, staked)	Unknown
Syringe Volume	1 ml
Device materials including lubricant	Syringe Barrel is (b) (4) Type I glass. (b) (4) needle, (b) (4) Plunger stopper needle shield P (b) (4) Rigid needle shield (b) (4) See table 2 above and 3.2.P drug-product p. 36/41

Additional Syringe Description/Requirements

Requirement	Reviewer Comment
Hypodermic Needle: length, gauge, and configuration of the tip.	1 mL long glass barrel with a ½ inch 27G (b) (4) needle with RNS
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility criteria (for insulin syringes). Insulin Syringes: The scale on the barrel should be in units of insulin.	The APFS does not contain graduation markings as it is intended to deliver the full labeled volume i.e., the APFS is single use for a fixed dose.
Reuse Durability (for reusable piston syringes): number of times the device can be sterilized and still meet specifications (using sterilization method indicated in the labeling).	N/A
Safety Features (e.g. Needle safety component/device)	The PFS-SA is assembled with a needle safety guard to protect the user from unintended needle stick injuries. The needle safety guard design provides (b) (4) of the safety mechanism to cover the needle following injection.
Automated Functions	N/A
Sterilization method	N/A

*See Design Verification Section for verification of design requirements

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor provided an adequate device deciption for the Pre-Filled Syringe prefilled (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☑

5.1. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☐ Yes ☐ No ☑ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection Needed ☐ N/A
CDRH completed a review of the Quality Systems	☐ Yes ☐ No ☐ N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in Appendix B

5.2. Filing Recommendation

FILING REVIEW CONCLUSION
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☑ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☑ N/A **Site(s) needing inspection:**
Reviewer Comments
Refuse to File Deficiencies: ☐ Yes ☐ No ☑ N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No ☑ N/A

☐ **No Additional Information Requests to add**

6. DEVICE PERFORMANCE REVIEW

6.1. Design Verification/Validation

6.1.1. Device Specification Standards and Guidance Documents

Syringe		**Data Adequate**		
		Yes	**No**	**N/A**
Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☑	☐	☐
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☐	☐	☑
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☑
Needle/Sharps		**Data Adequate**		
		Yes	**No**	**N/A**
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☐	☐	☑
Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☐	☐	☑
Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	☐	☐	☑
Luer Lock		**Data Adequate**		
		Yes	**No**	**N/A**
Connection	ISO 80369-7, Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications **(replaces ISO 594-1 and 594-2 as of 2020) ISO 594-1, Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 1: General requirements ISO 594-2, Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 2: Lock fittings	☐	☐	☑
Other		**Data Adequate**		
		Yes	**No**	**N/A**
[Other]	[Other]	☐	☐	☐

6.1.2. Device Performance Evaluation

3.2.R Device Design Verification

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy/ Delivered Volume	The combination product shall deliver a dose volume (b) (4) mL	Y. Accept of 95%C/97.5%Rtol erance interval, V (b) (4) mL Results: n = 60 min = (b) (4) max = mean StDev	Y. Data provided to support dose volume (b) (4) mL in 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/97.5%Rtol erance interval, V (b) (4) mL. n = 60 min = (b) (4) max = mean StDev
Break loose Force	Maximum break loose force (b) (4)	Y. A constant injection rate/ compression speed (b) (4) mm/min) is applied to each syringe tested. Accept on 95%C/90%R tolerance interval, Requiring a sample size of 60, F (b) (4) N Results:n = 60 min = 5N max = 8N mean = 7N StDev = 1N	Y. Data provided to support Maximum break loose force (b) (4) N in 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/90%R tolerance interval, F (b) (4) N. n = 29 min = 6N max = 9N mean = 7N StDev = 1N
Glide Force	Maximum glide force (b) (4)	Y. A constant injection rate/ compression speed (b) (4) mm/min) is applied to each syringe tested. Accept on 95%C/90%R tolerance interval, Requiring a sample size of 60, F (b) (4) Results: n = 60 min = 6N	Y. Data provided to support Maximum glide force (b) (4) in 3 lots	Y. Data is supported for up to 60 months real-time aging at storage conditions of 5°C	Y. Accept on 95%C/90%R tolerance interval, F (b) (4) N. n = 29 min = 6N max = 8N mean = 7N

		max = 9N mean = 8N StDev = 1N			StDev = 0N
Cap Removal Force	Not applicable	N/A		n/a	n/a
Rigid needle shield pull-off force	The combination product shall have a rigid needle shield pull-off force that is (b) (4)	Y. 95%C/90%R tolerance interval, (b) (4) Results: n = 46 min = 18N max = 24N mean = 21N StDev = 1N	Y. Data provided to support rigid needle shield pull-off force that is (b) (4) in 3 lots	N/A	Y. Accept on 95%C/90%R tolerance interval, (b) (4). n = 46 min = 18N max = 23N mean = 21N StDev = 1N
Needle safety feature activation	(b) (4)	Accept on 0 failures. Reject on 1 or more failures	n = 29 pass = 29 fail = 0	N/A	Accept on 0 failures. Reject on 1 or more failures n = 29 pass = 29 fail = 0
Needle access after injection		(b) (4) Accept on 0 failures. Reject on 1 or more failures	n = 29 pass = 29 fail = 0	N/A	n = 29 pass = 29 fail = 0
Needle safety feature override force after injection		Accept on 95%C/90%R tolerance interval, F (b) (4)	n = 29 min = 141N max = 153N mean = 146N StDev = 3N	N/A	n = 29 min = 116N max = 135N mean = 124N StDev = 4N

Device Free Fall	(b) (4)	No breakage to PFS-SA Accept on 0 failures. Reject on 1 or more failures Deliverable volume V (b) (4) mL Accept on 95%C/97.5%R tolerance interval, V (b) (4) mL (b) (4) Accept on 0 failures. Reject on 1 or more failures	n = 40 pass = 40 fail = 0 min = 1.0mL max = 1.1mL mean = 1.1mL StDev = 0.0mL n = 40 pass = 40 fail = 0	N/A	N/A

Reviewer Comment

The device design verification testing is acceptable. Results include dose accuracy/Delivered volume, Break Loose Force, Glide Force, and Rigid needle shield pull-off force.

3.2.P.2.4.2.4 Performance

"The essential performance requirements of the combination product was evaluated via functionality (break loose and glide force) and deliverable volume tests that were performed as part of specified Drug Product stability studies (M3.2.P.8.1). A summary of the initial (time zero) results are shown in Table 9. The results show that the maximum break loose force, maximum glide force, and deliverable volume were reproducible and consistent between Drug Product lots. The performance of the container closure system was demonstrated to be suitable for injection." P. 16, 3.2.P.2.4 Container Closure System

Table 9 Summary of Container Closure Performance

Stability Lot Number (Stability Protocol Number)	Maximum Break Loose Force (N)	Maximum Glide Force (N)	Deliverable Volume (mL)
83205.145 (DSP-35436)	(b) (4)		
002G13 (DSP-35437)			
ML00029-35 (DSP-354309)			

Analytical procedures for Break Loose Force and Glide Foce is summarized in 3.2.P.5.2 Analytical Procedures

6.1.3. Stability Review Summary

Shelf-life:	shelf life of 36 months for drug product
Storage **conditions**:	storage condition of 5°C
Time period and storage conditions provided for accelerated aging:	25°C ± 2°C/60% ± 5% RH is an accelerated condition
Time period and storage conditions provided for real-time aging:	Storage condition of 5°C with testing scheduled at 0, 3, 6, 9, 12, 18, 24, 36 months and with additional 48 and 60 months for some primary lots. (3.2.P stability summary)

*Endpoint evaluation is provided in section 6.1.2.

Stability studies are monitored at four conditions:

- (b) (4) condition evaluates stability at the temperature at which the Drug Substance is stored (long-term storage condition)
- (b) (4) C condition evaluates stability at a short term recommended storage condition
- (b) (4) % RH is an accelerated condition
- (b) (4) % RH is a stressed condition

3.2.S.7.1 Stability Summary and Conclusions

The proposed Drug Substance shelf life is (b) (4) months at the long-term storage condition of (b) (4) in (b) (4) based on the follow g:

- [redacted] months of existing real time data on commitment lots.
- [redacted] months of real-time data from 2 primary lots (BL2136, 72635-106), [redacted] months of realtime data from 3 more primary lots (HL2758, HL2777, HN2204), and [redacted] months of realtime data from 1 more primary lot (KJ0190).

The proposed Drug Substance shelf life is [redacted] months at the short term storage condition of [redacted] C in [redacted] based on the following:

- [redacted] months of real time data on commitment lots.
- [redacted] months of real-time data from primary lots (BL2136, 72635-106, HL2758, HL2777, HN2204, and KJ0190).

The proposed Drug Substance shelf life is [redacted] months in total in [redacted] This [redacted] months may be apportioned under a combination of two storage conditions as follows:

- [redacted] months at the long-term storage condition of [redacted] C.
- [redacted] months at the short-term storage condition of [redacted] C, noting Drug Substance may [redacted]

Statistial justification of a sample size of N=60 is provided in 3.2.R.3.4 Design Verification Overview

3.2.P.8.3 Stability Data

From three separate lots:
Real time aging under recommended storage conditions of 5°C is provided for 60 months. This is enough to support the 36 month shelf life. BLF abd GF samples below. Dlivered Volume was also supported up to 60 months with dose volume [redacted] mL

Table 3 Stability Results for Primary Lot 011G13A (150 mg/mL): Device Functionality Testing

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
Acceptance criteria	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)
5°C ± 3°C							
0	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]	NP[a]
3	[redacted]						
6							
12							
18							
24							
36							
48							
60							
25°C ± 2°C / 60% ± 5% RH							
0							
1							
3							
6							

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
40°C ± 2°C / 75% ± 5% RH							
0							
1							
3							

(b) (4)

RH = relative humidity;

NP = not performed per the stability protocol

[a] Initial timepoint testing for rigid needle shield removal force and break loose glide force assays were inadvertently not performed. Investigation was conducted and the root cause was inadequate documentation upon shipment of samples for testing.

Table 3 Stability Results for Primary Lot 83205.145: Device Functionality Testing

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
Acceptance criteria	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)	Report Results (N)
5°C ± 3°C							
0							
3							
6							
12							
18							
24							
30							
36							
42							
48							
60							
25°C ±2°C / 60% ± 5% RH							
0							
1							
3							
6							

(b) (4)

Time (months)	Rigid Needle Shield Removal Force			Break Loose		Glide Force	
	Minimum	Maximum	Median	Median	Maximum	Median	Maximum
40°C ± 2°C / 75% ± 5% RH							
0							
1							
3							

(b) (4)

RH = relative humidity

Reviewer Comments

The sponsor provides stability data for the device with evaluation of shield removal force, Break loose force, and Glide force. The results are acceptable.

The device has (b) (4) needle safety device. The sponsor appears to have evaluated this function per the ISO 23908 standard. Some functions include; Needle safety activation, Needle safety lockout. Both need to be verified after shelf-life, shipping and drop testing. Reliability should be 99%, not 90% per FDA guidance (https://www.fda.gov/media/71142/download)

Needle safety may have been covered through glide force but the reliability should be 99%, not 90% per FDA guidance (https://www.fda.gov/media/71142/download)

An IR is recommended:

1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons:

   The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required.

   Furthermore, the testing should also be performed afrer aging of the device, dropping of the device, and simulated shipping.

   This confidence and reliability information for sharps injury prevention devices can be found in *FDA Guidance: Medical Devices with Sharps Injury Prevention Features* https://www.fda.gov/media/71142/download

An IR was issued December 14, 2020 in CR#3. The response was not adequate. The sponsor provided documentation of the testing of the (b) (4) which was approved through 510(K). This teting is provided, however, the testing does not appear to include any testing with aging of the device (Shelf-Life), dropping of the device, and simulated shipping. It is not clear if the testing is the final manufactured design of the proposed device. Needle safety performance needs to be tested on the final finished combination product because the prefilled syringe, combination product manufacturing and preconditioning may impact the performance.

6.1.4. Biocompatibility Evaluation

☑ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]

☐ Biocompatibility was not evaluated **because**: Click or tap here to enter text.

Contact Type and Duration:	Surface-contacting, skin – limited exposure up to 24 h.
Test article:	Syringe Barrel, Needle, Needle adhesive, Plunger stopper, Rigid Needle Shield, (b) (4) (b) (4)
Endpoints Evaluated:	Cytotoxicity, Skin sensitization, Systemic Toxicity (Pyrogenicity), Selection of tests for interactions with blood (not specified)

Extraction Method and Test Methods Acceptability:	Report not provided.

Reviewer Comment

The sponsor claims conformance to Biocompatibility testing (ISO 10993), however, the reports of the testing are not provided. The syringe barrel, , Needle, Needle adhesive, Plunger stopper, are within the fluid patch of the drug and an evaluation of these components is deferred to CDER. However, the Extended finger flange, Needle safety guard, and Plunger rod are not in direct contact with the drug substance and will be evaluated as part of this memo. The sponsor notes Cytotoxicity and Skin sensitization testing, that the testing conforms to the criterion of ISO 10993, however reports are not provided. Classification for the device as a surface device contacting intact skin (Per the 2016 FDA guidance Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" and ISO 10993-1, the Sponsor should evaluate the following endpoints for the plunger: Cytotoxicity, Sensitization, and Irritation. Since the Sponsor has not submitted any report all reports should be submitted. Furthermore,the sponsor does not indicate that skin irritation testing has been performed on the skin contacting components. An information request will be issued to the Sponsor.

Table 16 Primary packaging component materials

Component	Description	Material of Construction	Compliance
Syringe barrel		Type I (b) (4) glass	USP <660>, Ph. Eur 3.2.1, and JP 7.01
Needle	(b) (4)	(b) (4)	ISO 9626
Rigid needle shield (b) (4)			
Rigid needle shield (b) (4)			USP <381> and Ph. Eur. 3.2.9
Adhesive			USP <88>
(b) (4)			(b) (4) Ph. Eur. 3.1.8
Plunger stopper	(b) (4)		USP <381>, USP <87>, USP <88> and Ph.Eur 3.2.9.
(b) (4)			(b) (4) Ph. Eur. 3.1.8

Table 17 Device components

Accessory component	Material of Construction	Compliance
Needle safety guard	(b) (4)	ISO 10993 materials for surface contact <24 hours
Extended finger flange		ISO 10993 materials for surface contact <24 hours
Plunger rod		ISO 10993 materials for surface contact <24 hours

	Date Sent: 10/2/2020	Date/Sequence Received: 10/30/2020
Information Request #1	1. For the extended finger flange, needle safety guard, and plunger rod, which are intact skin contacting, you provide Cytotoxicity and Skin sensitization testing, that you indicate conforms to the criterion of ISO 10993, however you do not provide	

<table>
<tr><td></td><td>reports to verify that conformance. Furthermore, per FDA guidance Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process” the appropriate endpoints based on your contact classification are: Cytotoxicity, Sensitization, and Irritation. Therefore, please provide testing reports for cytotoxicity, sensitization, and irritation for the extended finger flange, needle safety guard and plunger rod.</td></tr>
<tr><td>Sponsor Response</td><td>The device components extended finger flange, needle safety guard and plunger rod have been tested for cytotoxicity, sensitization and irritation according to ISO 10993-5 “Biological Evaluation of Medical Devices Part 5: Tests of In Vitro Cytotoxicity” and ISO 10993-10 “Biological Evaluation of Medical Devices Part 10: Tests for Irritation and Skin Sensitization” Reports containing the results of biocompatibility testing to verify conformance with ISO 10993 are included in module 3.2.R.3.5.3.</td></tr>
<tr><td>Reviewer Comments</td><td>The sponsor provided summary test reports in the response Module 3.2.R.3.5.3 Device Biological Evaluation, Reg-info-dbe and files with Nov. 1, 2020 response. The sponsor tested the finger flange, needle safety guard, and plunger rod for biocompatibility with in vitro Cytotoxity, Skin Irritation, and Skin sensitization according to ISO 10993, part 5 and part 10 as appropriate.

The plunger rod reported in reg-info-cs-01
Studies results summary for TA_12T_50471 (b) (4) Plunger Rod): qualification of the (b) (4) plunger rod.

IN VITRO STUDIES, Test Article 12T_50471
<table><tr><th>Test</th><th>Results</th></tr><tr><td>ISO 10993-5
Cell Cytotoxicity Elution Test</td><td>Cytotoxicity: none
Score = 0</td></tr></table>
IN VIVO STUDIES, Test Article 12T_50471
<table><tr><th>Test</th><th>Results</th></tr><tr><td>ISO 10993-10
Intracutaneous Reactivity</td><td>Negligible Irritant
Score = 0.0 (SAL) / Score = 0.1 (SO)</td></tr><tr><td>ISO 10993-10
Guinea Pig Maximization Test</td><td>Nonsensitizer
Score = 0 (SAL, SO)</td></tr></table>
The needle safety guard reported in reg-info-cs-02</td></tr>
</table>

***IN VITRO* STUDIES, Test Article 17-6200-016**

Test	Results
ISO 10993-5 Cell Cytotoxicity Elution Test	Cytotoxicity: none Score = 0

***IN VIVO* STUDIES, Test Article 17-6200-016**

Test	Results
ISO 10993-10 Primary Dermal Irritation	Negligible Irritant PII = 0 (SAL, SO)
ISO 10993-10 Guinea Pig Maximization Test	Nonsensitizer Grade = 0 (SAL, SO)

The finger flange reported in reg-info-cs-03

Studies results summary for TA 13T_58642 [redacted]^(b) (4) **finger flange): qualification of the** [redacted]^(b) (4) **finger flange.**

***IN VITRO* STUDIES, Test Article 13T_58642**

Test	Results
ISO 10993-5 Cell Cytotoxicity Elution Test	Cytotoxicity: none Score = 0

***IN VIVO* STUDIES, Test Article 13T_58642**

Test	Results
ISO 10993-10 Intracutaneous Reactivity	Negligible Irritant Score = 0 (SAL,SO)
ISO 10993-10 Guinea Pig Maximization Test	Nonsensitizer Score = 0 (SAL, SO)

The response is adequate.

Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

6.1.5. Sterility Evaluation

☐ Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)
☑ Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

6.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: ☐ **Yes** ☐ **No** ☐ **N/A**	**Mid-Cycle Deficiencies:** ☑ **Yes** ☐ **No** ☐ **N/A**	**Final Deficiencies:** ☐ **Yes** ☐ **No** ☐ **N/A**

Reviewer Comments
The sponsor has not conducted testing after simulated shipping that is representative of the Sponsor's distribution channels.
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No

	Date Sent: 10/2/2020	**Date/Sequence Received:** 10/30/2020
Information Request #2	2. You do not provide testing demonstrating the functionality of your prefilled syringe after simulated shipping. Pleaae provide performance data for your essential performance requirements (i.e., breakloose/glide force and dose accuracy) after simulated shipping representative of your distribution channels.	
Sponsor Response	The tralokinumab drug-device combination product was subjected to simulated shipping per ASTM D4169 and functionality testing of the pre-filled syringe was conducted as part of design verification after simulated shipping. A summary of test results was provided in BLA 3.2.R.3.4 Design Verification, Table 5. This information was sent to the FDA on 06 October 2020 as part of LEO Pharma's responses to the Mid-Cycle Communication Agenda received on 01 October 2020. On 08 October 2020, the FDA confirmed that LEO Pharma's response was adequate to address the FDA request.	
Reviewer Comments	The requested testing was provided in 3.2.R.3.4 Design Verification. The Sponsor provided a new simulated shipping protocol and stated that the new protocol is representative of its distribution channels. Data to demonstrate that the device will perform adequately inclided functionality testing of the pre-filled syringe was conducted as part of design verification after simulated shipping. The simated shipping testing is acceptable.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** 12/14/2020	**Date/Sequence Received:** 12/21/2020
Information Request #3	1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons: The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required. Furthermore, the testing should also be performed after aging of the device, dropping of the device, and simulated shipping. This confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download	
Sponsor Response	(Series 0022)LEO Pharma's response to the information request is included in module 1.11.1. The following new module 3.2.R documents were added to the eCTD: • 3.2.R.3.4.7 Executive Summary safety Claim (b) (4) Needle Guard • 3.2.R.3.4.7 Summary FDA ISO 23908 (b) (4) 510k • 3.2.R.3.4.7 Quality Statement ISO 23908 (b) (4)	

	Summary of FDA Guidance/ISO 23908 Bench Testing Filed in (b) (4) needle guards 510(K)s In 100% of the 512 tested (b) (4) devices the guard completely covered the needle and the lock-out feature was 100% effective; therefore, zero failure was recorded in the present study. The acceptance criteria from the ISO 239081 and FDA guidance2 on sharps injury prevention feature (i.e. zero device failures out of 500 devices activation) was met.
Reviewer Comments	The sponsor provided documentation of the testing of the (b) (4) which was approved through 510(K). This teting is provided, however, the testing does not appear to include any testing with aging of the device (Shelf-Life), dropping of the device, and simulated shipping. It is not clear if the testing is the final manufactured design of the proposed device.
Response Adequate:	☐ **Yes** ☑ **No, See CR 1# Sent on** Click or tap to enter a date.

Device	Submission Type	510(K)	510(K) Clearance Date	Stimulated Clinical Use Testing Filed with FDA (510(k) Reference Section)
(b) (4) needle guard	Traditional 510k	(b) (4)	5/29/2001	As per FDA Draft Supplementary Guidance on the *Content of Premarket Notification {510(k)} Submissions for Medical Devices with Sharps Injury Prevention Features*, March 1995, each of the specified acceptance criteria in the controlled simulated clinical use test were either met or exceeded. Stimulated clinical trials were based on predicative devices (b) (4) series. (b) (4)
(b) (4) {Expansion of Indications for Use}	Traditional 510k		4/28/2006	No additional sharps injury prevention testing required for this premarket notification.
(b) (4) needle guard {New Materials for Plunger Rod}	Special 510k		9/20/2012	As per FDA Guidance *Medical Devices with Sharps Injury Prevention Features*, "If your sharps injury prevention feature is currently legally marketed as a part of another device, you may identify that device in lieu of performing simulated clinical use testing." SSI relies on the clinical use studies completed for the legally marketed devices as well as additional simulated use study for the addition of the various plungers. As per FDA guidance and ISO 23908, 168 devices were tested with zero failures. (b) (4)
(b) (4) (b) (4) needle guard {New Design}	Traditional 510k		3/26/2013	As per FDA Guidance *Medical Devices with Sharps Injury Prevention Features*, 500 devices were tested with zero failures for a *"97.5% confident that the true failure rate was no higher than 0.7% and 99.5% confidence that it is no higher than 1.1%"*. (b) (4)
(b) (4)				

7. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)

Dose Accuracy	The combination product shall deliver a dose volume (b) (4) mL	Y
Break loose Force	Maximum break loose force (b) (4)	Y
Glide Force	Maximum glide force (b) (4)	Y
Cap Removal Force	N/A	N/A
Rigid need;e shield pull-off force	The combination product shall have a rigid needle shield pull-off force that is (b) (4)	Y

Reviewer Comments

The Sponsor has included the EPRs of the device constituent parts of the combination product in the release testing of the device. This is an acceptable control strategy. The needle safety activation was notadequately evaluated. An IR was sent on December 14, 2020, however, the sponsor presented a resppnse based on prior approval of the device through the 510(k) process, however, testing for shelf-life and shipping is needed with the current PFS product. A major deficiency is recommended.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

7.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

The sponsor provided an adequate device desciption for the Pre-Filled Syringe prefilled (APFS) which administers a 1 mL (150 mg/mL) of tralokinumab. The APFS is a single-use, disposable, needle-based injection system with (b) (4) needle safety function. The sponsor had conducted performance testing of the device demonstrating that the device met Essential Performance Requirements for validation, after simulated shipping, and aging(shelf-life). While the sponsor provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. The testing is not adequate mostly for sample size and reliability of the needle safety feature which is essential for preventing accidental needle sticks.

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Filing/74-Day Information Requests

8.2. Mid-Cycle Information Requests

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

1. For the extended finger flange, needle safety guard, and plunger rod, which are intact skin contacting, you provide Cytotoxicity and Skin sensitization testing, that you indicate conforms to the criterion of ISO 10993, however you do not provide reports to verify that conformance. Furthermore, per FDA guidance *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"* the appropriate endpoints based on your contact classification are: Cytotoxicity, Sensitization, and Irritation. Therefore, please provide testing reports for cytotoxicity, sensitization, and irritation for the extended finger flange, needle safety guard and plunger rod.
2. You do not provide testing demonstrating the functionality of your prefilled syringe after simulated shipping. Pleaae provide performance data for your essential performance requirements (i.e., breakloose/glide force and dose accuracy) after simulated shipping representative of your distribution channels.

8.3. Interactive Information Requests

8.3.1. Interactive Information Requests sent on 12/14/2020

1. You provided performance testing in the Device Design Verification for the needle safety device, specifically evaluating Essential Performance Requirements of Needle safety feature activation, needle access after injection, Needle safety feature override force after injection, and Device Free Fall. However, the testing is not adequate for the following reasons:

   The reliability and sample size is not acceptable. Please analyze the data assuming confidence interval of 95% with 99% reliability. Please provide the sample size to demonstrate the confidence interval and reliability required.

   Furthermore, the testing should also be performed after aging of the device, dropping of the device, and simulated shipping.

   This confidence and reliability information for sharps injury prevention devices can be found in FDA Guidance: Medical Devices with Sharps Injury Prevention Features https://www.fda.gov/media/71142/download

9. APPENDIX B: FACILITIES & QUALITY SYSTEMS REVIEW

9.1. Facility Inspection Report Review

Facility Regulatory History Review	
Firm Name:	
Address & FEI:	
Responsibilities:	
Site Inspection Recommendation:	Choose an item..

Reviewer Comments

Add Facility

☐ **No Additional Facilities**

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☐ Yes	☐ No

9.2. Quality Systems Documentation Review

9.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

Reviewer Comments

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☐Yes	☐No

9.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:
☐ Device QSR-based

☐ Drug cGMP-Based Streamline – Review Instructions
☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s):	**Reviewer Discussion** –
21 CFR 820.30 Summary of Design Controls	Firm(s):	**Reviewer Discussion** – Reviewed in detail in Section 6
21 CFR 820.50 Summary of Purchasing Controls	Firm(s):	**Reviewer Discussion** –
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s):	**Reviewer Discussion** – Reviewed in Section 9.2.3.
21 CFR 820.170 Summary of Installation	Firm(s):	**Reviewer Discussion** –
21 CFR 820.200 Summary Servicing	Firm(s):	**Reviewer Discussion** –
Subpart F – Identification and Traceability	Firm(s):	**Reviewer Discussion** –
Subpart G – Production and Process Controls	Firm(s):	**Reviewer Discussion** – Reviewed in Section 7
Subpart H – Acceptance Activities	Firm(s):	**Reviewer Discussion** –
Subpart I – Nonconforming Product	Firm(s):	**Reviewer Discussion** –
Subpart K – Labeling and Packaging Controls	Firm(s):	**Reviewer Discussion** –
Subpart L – Handling, Storage, Distribution	Firm(s):	**Reviewer Discussion** –

Subpart M – Records	Firm(s):	**Reviewer Discussion** –
Subpart O – Statistical Techniques	Firm(s):	**Reviewer Discussion** –

Reviewer Comments

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☐ Yes	☐ No

9.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	**Present**
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	
Investigations into the cause of nonconformities relating to product, processes, and the quality system	
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	
Requires documentation of all CAPA activities	

Reviewer Comments

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☐Yes	☐No

9.3. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Facilities & QS Review Section**

10. APPENDIX C (CONSULTANT MEMOS)

10.1. Insert Discipline Review Memo – Insert Consultant Name

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: December 1, 2020 **Date consulted:** October 8, 2020

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: (b) (4) (tralokinumab) injection for subcutaneous use

BLA: 761180

Applicant: LEO Pharma A/S

Subject: Evaluation of post-marketing requirements (PMRs)

Indication: For the treatment of moderate-severe atopic dermatitis (AD) in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable

Materials Reviewed:

- DPMH consult request dated October 8, 2020, DARRTS reference ID 4683300
- Applicant's submitted background package and proposed labeling for BLA 761180, submitted April 27, 2020
- Applicant's draft outline of the pregnancy post-authorization study (PASS), submitted October 14, 2020

- Applicant's response to DPMH's information request (IR) to provide additional information to comply with the Pregnancy and Lactation Labeling Rule for BLA 761180, submitted October 29, 2020
- DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992[1]

Consult Question: "Provide assistance in evaluating the need for a prospective registry of pregnancy/ fetal/ infant observational exposure cohort study and a retrospective cohort study of pregnancy outcomes for tralokinumab exposure and a non-tralokinumab systemic therapy or phototherapy exposure cohort."

INTRODUCTION AND BACKGROUND

On April 27, 2020, LEO Pharma A/S submitted an original 351 (a) biologic license application (BLA). (b) (4) (Tralokinumab) is a new molecular entity. The proposed indication is the treatment of moderate-severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. On October 8, 2020, DDD consulted the DPMH to provide recommendations for possible pregnancy and lactation PMRs.

Regulatory History

- Tralokinumab is a fully human immunoglobulin G subclass (IgG4) monoclonal antibody to IL-13. Tralokinumab is not currently approved for any indication but has been investigated in the treatment of AD, asthma, ulcerative colitis, and idiopathic pulmonary fibrosis. There are no approved anti-IL-13 antibodies.
- 2017: Dupilumab was approved as the first biologic for first-line treatment for moderate-severe AD. Dupilumab is a human monoclonal IgG4 antibody that binds to the IL-4 Rα subunit and inhibits IL-4 and IL-13. Known adverse reactions include hypersensitivity reactions and conjunctivitis. Current data in pregnancy are limited to one published case report[2,3] and a limited number of cases from clinical trials.[4] There are no known safety issues for dupilumab use in pregnancy and there is an ongoing pregnancy exposure registry to monitor pregnancy outcomes.
- October 15, 2020: FDA sent an IR for additional information to comply with the Pregnancy and Lactation Labeling Rule for BLA 761180. The IR was received from the applicant on October 29, 2020.

[1] The Dupixent review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2] Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. J Eur Acad Dermatol Venereol. 2020:34(6):e256–7.
[3] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).
[4] DPMH labeling review for Dupixent, BLA 761055, January 13, 2017, Christos Mastroyannis, MD, Medical Officer, DARRTs reference ID: 4041992

Drug Characteristics[5]

- Tralokinumab[6] is a fully human IgG4 monoclonal antibody that neutralizes IL-13 by inhibiting the interactions with the IL-13 receptors. IL-13 is a cytokine involved in the altered immune response in AD
- Dose and administration: initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week. Tralokinumab is supplied as a 1 ml single dose prefilled syringe containing 150 mg/ml solution for subcutaneous injection
- Bioavailability: 76%
- Half-life: (b) (4)
- Molecular weight: 147 kilodaltons
- Adverse reactions: upper respiratory infection, conjunctivitis, injection site reaction, and eosinophilia

REVIEW

PREGNANCY

AD and Pregnancy

Data on the prevalence of AD in adults in the United States are limited but it is estimated up to 10% of adults in high-income countries are affected.[7] Approximately half of the AD population are females and AD affects all age groups. It is estimated that 44-57% of adult patients with AD have moderate disease and 12-21% have severe disease based on the Patient Oriented Scoring of Atopic Dermatitis. Systemic immunomodulating therapies may be needed in those with moderate-severe AD.[8]

First-line treatments during pregnancy include skin hydration (e.g., emollients) and topical therapies (i.e., corticosteroids, calcineurin inhibitors, ultraviolet light therapy). In cases of severe or refractory disease, systemic therapies (e.g., short course of corticosteroids, calcineurin inhibitors) may be used. The literature on systemic treatments (e.g., dupilumab and other biologics in development) during pregnancy is sparse. [9, 10]

Nonclinical Experience

In two pre and post-natal developmental studies of pregnant monkeys who received tralokinumab (up to ten times the maximum recommended human dose), there was no embryofetal toxicity or adverse developmental effects noted in the offspring.

[5] Applicant's proposed labeling for (b) (4) August 2020

[6] Previously referred to as CAT-354 and LP0162

[7] Langan, S, Irvine, A, Weidinger, S. Atopic dermatitis. Lancet 2020, 396, 345–360

[8] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).

[9] Heilskov, S., Deleuran, M.S. & Vestergaard, C. Immunosuppressive and Immunomodulating Therapy for Atopic Dermatitis in Pregnancy: An Appraisal of the Literature. *Dermatol Ther (Heidelb)* **10,** 1215–1228 (2020).

[10] Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: Section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71:327-49.

Review of Pharmacovigilance Database

The applicant searched their safety database of all completed and ongoing clinical trials using a cut-off date of October 22, 2020. The applicant identified 29 maternal pregnancies and 4 pregnancies with paternal exposure. In all cases where the pregnancy was continued, the mother discontinued tralokinumab treatment shortly after the pregnancy was reported.

The pregnancy outcomes for maternal exposure (n=29) are as follows:

- live births (n=12; no adverse infant outcomes)
- elective abortion (n=10; no fetal abnormalities specified)
- spontaneous abortion (n=2; no fetal abnormalities specified)
- ongoing (n=3)
- unknown (n=2)
- stillbirth (n=0)

The pregnancy outcomes for paternal exposure (n=4) are as follows:

- live births (n=2)
    - one infant had foot malformation and skull asymmetry, both described as mild.
- unknown (n=2)

The applicant concludes, "although no safety signals have been observed in relation to the use of tralokinumab during pregnancy, the information is limited to inform of maternal adverse reactions or drug-associated risk of adverse developmental outcomes."[11]

(b) (4)

[redacted]

[11] Applicant's clinical information amendment, submitted October 29, 2020

(b) (4)

[redacted]

DISCUSSION AND CONCLUSIONS

Pregnancy

AD is a common disease that affects up to 10% of adults and of those affected, it is likely more than half of these adults have moderate-severe disease for which systemic immunomodulators may be needed, including in females of reproductive potential. Indeed, even in clinical trials for AD where pregnant women were excluded and women were required to use contraception, there there were 29 reported pregnancies from maternal tralokinumab exposure and four pregnancies from paternal tralokinumab exposure.

There are currently no published data on tralokinumab use in pregnancy. In clinical trials, pregnant women were excluded and in the cases of pregnancies during the trial, tralokinumab was discontinued. Thus, while there are no safety concerns based on the current nonclinical and clinical data, these data are not adequate to assess the safety of tralokinumab use in pregnancy.

Given the anticipated use of tralokinumab in females of reproductive potential who may become pregnant, post-marketing studies are essential. There is currently not a disease-based registry for atopic dermatitis. DPMH recommends both a pregnancy registry study and complementary study. The applicant's proposed plan for a retrospective cohort study using electronic medical record data is an acceptable approach for a complementary study. DPMH also recommends a pregnancy exposure registry which would allow prospective data collection as well as information on potential confounders. For more information, the reader is referred to the May 2019 FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies.[13]

Lactation

There are no available nonclinical or clinical data regarding the presence of tralokinumab in milk, the effects on the breastfed infant, or the effects of the drug on milk production. Based on the lack of currently available data and the anticipated use of tralokinumab in pregnant and lactating women, DPMH also recommends a PMR for a clinical lactation study.

DPMH RECOMMENDATIONS FOR POSTMARKETING REQUIREMENTS (PMR)

DPMH recommends the following PMR language:

1. For the pregnancy exposure registry, the PMR description should include the following: A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tralokinumab during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

[13] FDA Draft Guidance for Industry: Postapproval Pregnancy Safety Studies. May 2019

2. DPMH agrees with the applicant's proposed plan for a retrospective cohort study using electronic medical record data, and recommends the following PMR description:
   An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to tralokinumab during pregnancy compared to an unexposed control population.
3. For the Clinical Lactation study, the PMR description should include the following:
   Perform a lactation study (milk only) in lactating women who have received therapeutic doses of tralokinumab using a validated assay to assess concentrations of tralokinumab in breast milk and effects on the breastfed infant.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 15, 2020
To:	Strother Dixon, PharmD Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD **Regulatory Review Officer** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	(b) (4) (tralokinumab-ldrm)
Dosage Form and Route:	Injection, for subcutaneous use
Application Type/Number:	BLA 761180
Applicant:	Leo Pharma Inc.

1 INTRODUCTION

On April 27, 2020, Leo Pharma Inc., submitted for the Agency's review a Biologics License Application (BLA 761180) for [redacted] (b) (4) (tralokinumab-ldrm) injection, for subcutaneous use, for the proposed indication of use in adults for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on May 11, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for [redacted] (b) (4) (tralokinumab-ldrm) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft [redacted] (b) (4) (tralokinumab-ldrm) PPI and IFU received on April 27, 2020, and received by DMPP on December 10, 2020.
- Draft [redacted] (b) (4) (tralokinumab-ldrm) PPI and IFU received on April 27, 2020, and received by OPDP on December 14, 2020.
- Draft [redacted] (b) (4) (tralokinumab-ldrm) Prescribing Information (PI) received on April 27, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 10, 2020.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
12/15/2020 12:34:57 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 11, 2020

To: Hamid Tabatabai, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
David Kettl, Clinical Team Leader, DDD
Strother Dixon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for (b) (4) (tralokinumab-ldrm) injection, for subcutaneous use

BLA: 761180

In response to DDD's consult request dated May 11, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), instructions for use (IFU) and carton and container labeling for the original BLA submission for (b) (4) (tralokinumab-ldrm) injection, for subcutaneous use (b) (4).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on December 9, 2020 and are provided below.

PPI and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 20, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 30, 2021

To: Hamid Tabatabai, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
David Kettl, Clinical Team Leader, DDD
Strother Dixon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for ADBRY™ (tralokinumab-ldrm) injection, for subcutaneous use

BLA: 761180

In response to DDD's consult request dated July 2, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and instructions for use (IFU) for the resubmission of the original BLA submission for ADBRY™ (tralokinumab-ldrm) injection, for subcutaneous use (Adbry).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI in Sharepoint on November 30, 2021 and are provided below.

PPI and IFU: OPDP's comments on the proposed labeling are based on the draft PPI and IFU in Sharepoint on November 30, 2021 and we have no additional comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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